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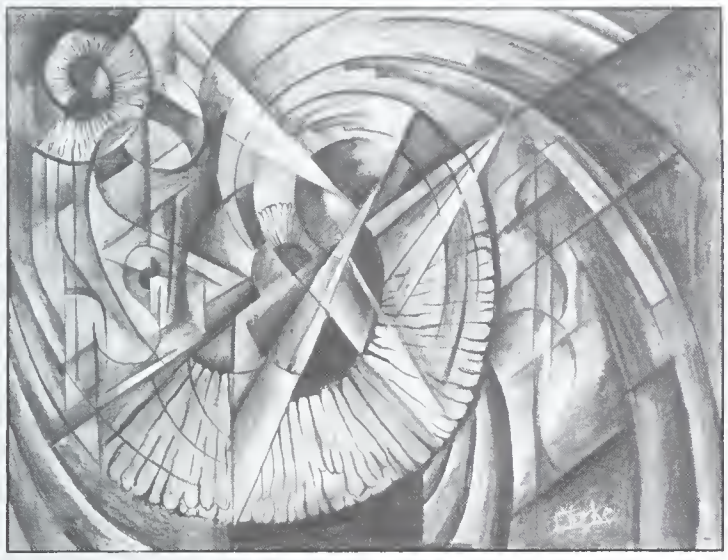

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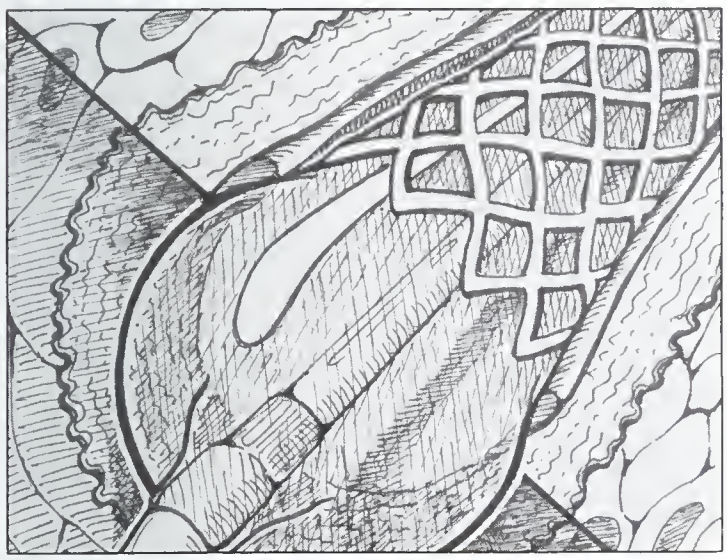

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Front cover: photo of retinal necrosis and hemorrhage as seen on funduscopy in a patient with CMV retinitis.

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Editorial

Dear Readers,

Despite the plethora of articles continuously being published on or related to the subjects of HIV and AIDS, the relevance and immediacy of this area of medicine has not diminished. Indeed, it is evident that the converse is true: as the prevalence of HIV increases, articles on this topic have become of practical interest in the broadest areas of medicine, from primary care to the most specialized subdisciplines.

Development of approaches to this disease have come from many directions. One of the most important has been the effort directed towards primary prevention, a concept illustrated in this issue by an article documenting the needle sharing practices among Toronto's street youth. An equally current and essential aspect is secondary complications of HIV infection. Our feature article reviews in detail the subject of CMV retinitis, a very common complication in AIDS patients. The article's discussion of the differential diagnosis of this condition and presentation of the latest advances in its management will hopefully prove valuable to physicians by helping them to recognize this treatable but potentially devastating entity.

An additional article in this issue that may attract widespread appeal concerns interventional procedures in cardiology. This excellent and comprehensive review outlines the entire range of techniques employed, from the advent of PTCA to the most recent advances in the field. Cardiac catheterization, a technique at the frontier of modern cardiology, is a subject that is relevant to students and clinicians alike.

In the previous issue, we reprinted a few pages from the May, 1925 UTMJ. We hope readers enjoyed this glimpse into the past. This month we have selected an article from the very first volume of the UTMJ entitled "The Discovery and Preparation of Insulin" by Frederick Banting and Charles Best.

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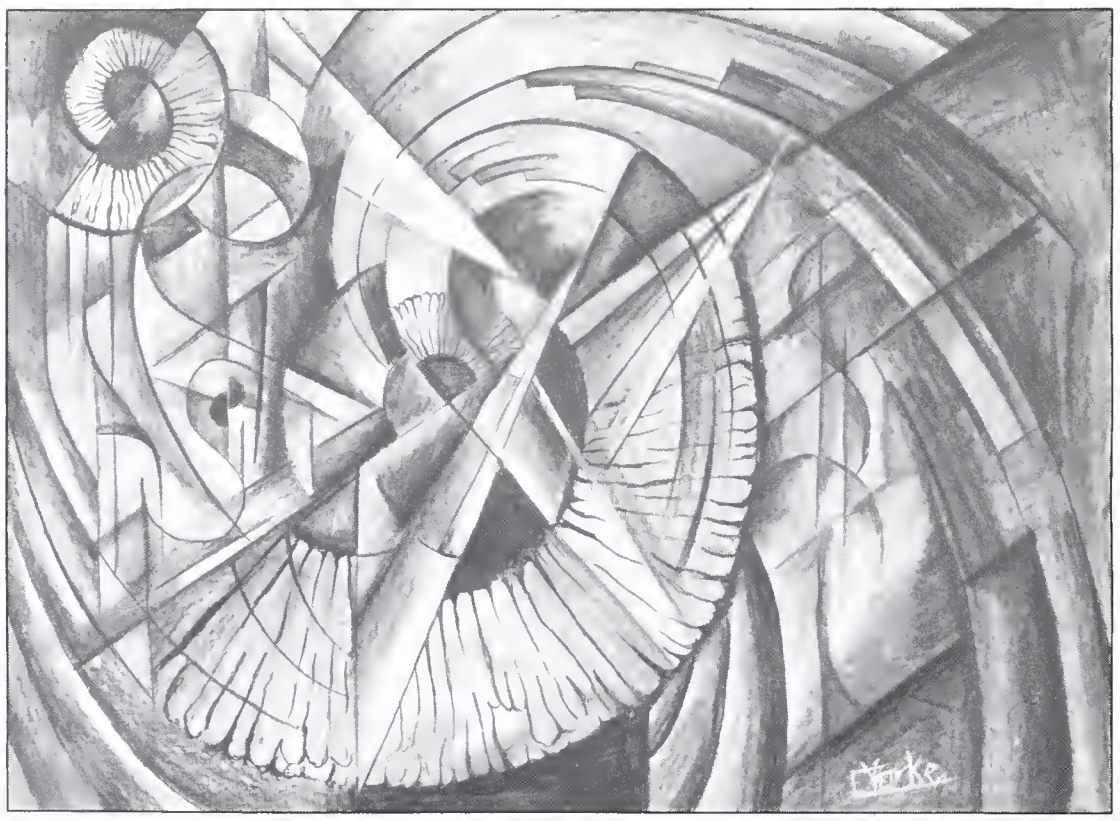
Lensectomy/Vitrectomy and Fluid/Silicone Oil Exchange for a Patient with a Double-Penetrating Oculo-Cerebral Trauma Caused by an Airgun Pellet

Alan Bau, 9T4, Nick George, M.B., F.R.C.S.*, and John D. Scott, M.B., F.R.C.S.**

*Senior Registrar, Addenbrookes Hospital, University of Cambridge School of Clinical Medicine, Cambridge, England
**Consultant Ophthalmic Surgeon, Ophthalmologist-in-Chief, Addenbrookes Hospital, University of Cambridge School of Clinical Medicine, Cambridge, England

Abstract

An 18 year-old female presented with a double-penetrating right eye injury caused by an airgun pellet. Computed tomography scan revealed the pellet lodged in the left basal ganglia. There was no resulting neurological deficit. Early globe repair was conducted, at which time retinal detachment was not present. Because of a marked cataract and massive vitreous clotting in the injured eye, a lensectomy/vitrectomy and fluid/silicone oil exchange was performed. One year post-trauma, the retina remained attached with a satisfactory visual outcome (6/60 with hyperopic correction) and no evidence of complications attributable to the silicone oil injection or the injury itself.



CHRIS YORKE

Introduction

We report a case of a double-penetrating oculo-cerebral injury caused by an airgun pellet managed by lensectomy/vitrectomy and fluid/silicone oil exchange. There are two main reasons for using silicone oil as an agent for prolonged intraocular tamponade. Firstly, its high viscosity refractive index (1.34) is similar to that of the ocular media, and secondly, the silicone oil's clarity and maintenance of volume allow better control of events in the post-operative period, without the need for frequent follow-up visits and re-injections associated with the use of gases[1]. One year post-trauma, the retina remained attached with a satisfactory visual outcome and no neurological deficit. This type of injury rarely carries a favourable prognosis. In Moore's study of ocular injuries associated with the use of airguns, all eyes (16) in the penetrating injury group caused by airgun pellets retained visual acuity less than counting fingers and 11 were ultimately ennucleated[2]. In addition, there has been no report to date suggesting the prophylactic use of silicone oil to prevent a retinal detachment in the management of double-penetrating ocular trauma.

Case Report

A previously healthy 18 year-old female presented to the hospital immediately after an airgun pellet injury to her right eye causing acute loss of vision in that eye. The shot occurred at close range, entering inferiorly and from the right side. Apart from minimal nausea and vomiting and right periorbital pain, the patient was otherwise asymptomatic; specifically, no associated loss of consciousness, seizures, weakness of limbs, or neck stiffness were observed. The patient was right-handed.

Neurological examination was completely unremarkable. Ophthalmic examination showed perforation of both the

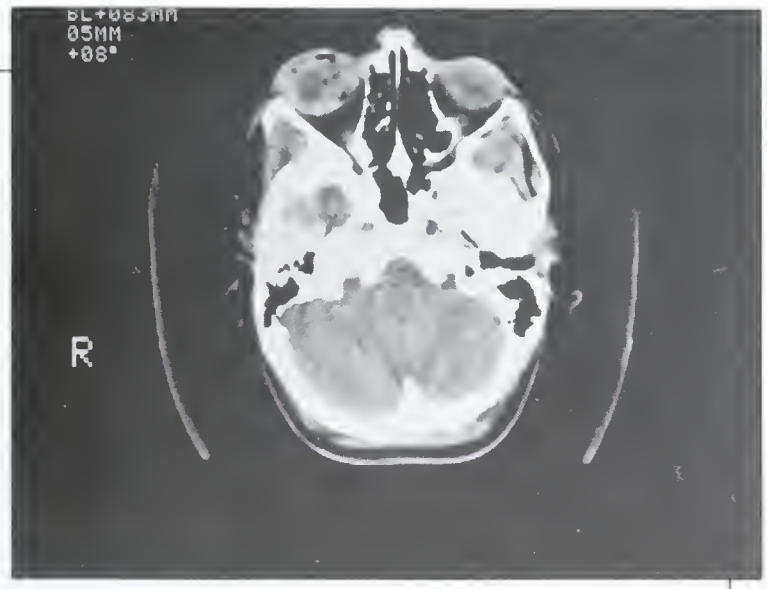


Figure 1: CT scan showing air pellet ocular entry site at the infero-medial aspect of the right eye.

right upper eyelid and right globe. Testing of the right visual acuity revealed only light perception with good projection in all quadrants. Extraocular movements were full.

Slit-lamp examination of the right eye revealed hyphema, a flat anterior chamber due to a swollen lens and leaking wound, and an inferior limbal laceration with marked iris prolapse. There was no red reflex in the right eye. The left eye displayed normal vision and no evidence of pathology.

CT scan revealed a pellet at the left basal ganglia in the left frontal-parietal lobes posterior to the coronal suture. The pellet was adjacent to the internal capsule and approximately 1.5 cm from the midline. A tiny hemorrhage and air locules were seen around the entry tract which traversed the globe of the right eye. There was no evidence of cerebral edema or hematoma (Figures 1, 2, and 3).

The patient was managed medically with phenytoin, cefotaxime, and metronidazole and surgically by immediate repair of the perforated right globe. During this operation, a right cataract with an inferior lens perforation was found. Also, a 1 cm long posterior globe perforation was discovered tracking backwards from the equator just superior to a hemorrhagic medial rectus. There was no obvious retinal or uveal prolapse. On post-operative day three, the anterior chamber was very shallow, the lens was touching the iris inferiorly, and the intraocular pressure (IOP) was normal (OD = 8 mmHg). At this time, testing of the visual acuity again indicated light perception with good projection in all quadrants. On post-operative day nine, in light of a marked cataract and massive vitreous clotting, a right pars plana lensectomy/vitrectomy and fluid/silicone oil exchange was performed. Since the original wound was leaking, scleral repair was also performed. Two days after this surgical procedure, the visual acuity of the right eye was sufficient to detect hand movements. The anterior chamber was deep, the retina (including the macula) was flat, the optic disc was edematous, and the IOP was normal (OD = 10 mmHg). In light of the difficult accessibility of the airgun pellet in the left cerebral hemisphere and the absence of any neurological deficit, it was decided at this point that the airgun pellet should be retained and followed with frequent neurological examinations.

One year post-trauma, the visual acuity of the right eye was 6/60 (Snellen's visual acuity measured in meters; equivalent to 20/200 measured in feet) with hyperopic correction. The silicone oil still remained in her eye. There was an area of scar tissue in the nasal retina, but the rest of the retina remained flat, being tamponaded by the silicone oil. There were no signs of sympathetic ophthalmia, which is a rare but devastating granulomatous bilateral uveitis developing after perforating eye injuries or ocular surgery. In addition, there was no evidence of complications resulting from silicone oil tamponade, a normal intraocular pressure (OD = 12 mm Hg), and no signs of keratopathy.

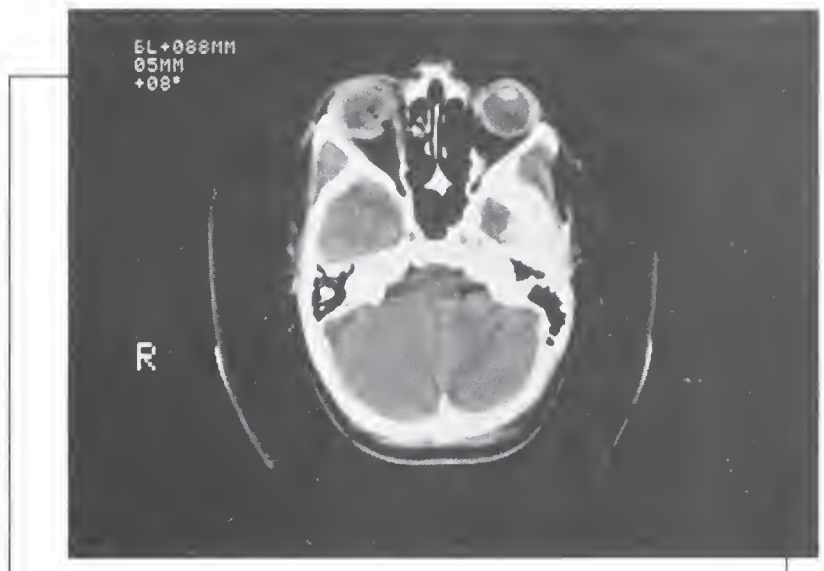


Figure 2: CT scan showing air pellet ocular exit site at the supero-medial aspect of the right eye adjacent to the medial rectus with intraocular air locules.

Discussion

Many reports have shown that double-penetrating ocular injuries have a poor visual prognosis[3,4,5]. The degree of damage incurred by the macula or optic nerve in severely

Figure 3: CT scan showing air pellet lodged at the left frontal-parietal lobes adjacent to the internal capsule and approximately 1.5 cm from the midline with no cerebral edema or hematoma.

injured eyes is the best predictor of visual outcome[6], while the main cause of a poor final visual outcome is a retinal detachment[7]. Cleary and Ryan demonstrated that the natural history of posterior penetrating eye injuries was a retinal detachment in most cases[8]. In ocular trauma, it has been shown that the growth of fibroblasts can cause traction on the retina resulting in retinal detachments[9]. It is now established that vitrectomy reduces the frequency of retinal detachments in perforating injuries of the globe by removing the scaffold along which fibroblasts proliferate[10,11].

In our patient, with no retinal detachment and no damage to the macula, optic nerve, or nervous system, the prognosis was favourable and hence, the main goal of therapy was to prevent a retinal detachment.

At present, the use of silicone oil as a prolonged intraocular tamponade is limited to the treatment of complex vitreoretinal disease[12]. In studies with complicated retinal detachments, silicone oil has been shown to be an effective tool for retinal support[13]. However, there are complications associated with the use of silicone oil as an intraocular agent. The most significant complication is the emulsification of the silicone oil. The emulsified silicone oil can obscure retinal details and may predispose to other complications such as glaucoma, cataract formation, and keratopathy[14]. In Riedel's study of 415 patients managed by intravitreal silicone oil injection and pars plana vitrectomy, complications such as silicone oil emulsification was seen in 0.7% of patients, keratopathy in 5.5% of patients, and glaucoma in 6.6% of patients[15]. However, Nawrocki has shown that silicone oil removal has a relatively high rate of complications, with the most frequent complication being retinal re-detachment[16]. According to Franks's study of 120 eyes managed by silicone oil removal, retinal re-detachment occurred in 19% of cases[17]. Furthermore, in most eyes within this study, cataract formation developed within 2 years despite early silicone oil removal (within 6 months), while glaucoma and keratopathy were occasionally reversed with silicone oil removal. It has been demonstrated that properties such as increased viscosity of the silicone oil[18] and avoidance of intraocular hemorrhage and inflammation[19] may have a role in decreasing the incidence of emuslification in prolonged silicone oil usage. At present, the optimal recommendations to remove silicone oil have not been clearly established. Taking into consideration the new and ill-defined risks associated with silicone oil removal, the exact criteria for the timing and safe removal of silicone oil after complex vitreoretinal surgery still need to be defined[20].

To our knowledge, there is no report of the combined prophylactic use of silicone oil and vitrectomy to prevent a retinal detachment in the management of penetrating ocular injury. At this time, the benefit of silicone oil and vitrectomy over vitrectomy alone in treating such injuries is inconclusive. Further studies, including long-term trials, need to be conducted in order to evaluate with greater certainty the efficacy of this combined treatment.

In light of the absence of any neurological deficit in our patient, no attempt was made to remove the pellet. In

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Jamjoom's study of airgun injuries of the brain, it is suggested that the removal of the pellet is dictated by its accessibility and the outcome depends on the intracranial structures involved and the development of complications[21]. Although there is a potential risk of systemic lead poisoning from a retained pellet, it is reported to be extremely rare[22].

In conclusion, a rare case of a double-penetrating oculocerebral trauma caused by an airgun pellet with a favourable prognosis is presented. Combined vitrectomy and fluid/silicone oil exchange may have a prophylactic role in the management of double-penetrating ocular injuries by preventing a retinal detachment.

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ERRATA

In the previous issue, the names of Dr. Tomas Salerno and Dr. George Trimble were inadvertently left off the list of patrons. We regret this oversight.

Also, in the article "The Mystery of Rett Syndrome", Daune MacGregor's name was misspelled. We apologize to Dr. MacGregor for the error.

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A Review of Cytomegalovirus Retinitis in AIDS Patients

Mona R. Loutfy, B.Sc. (9T5) and C. B. Mortimer, M.D., F.R.C.S.(C)*

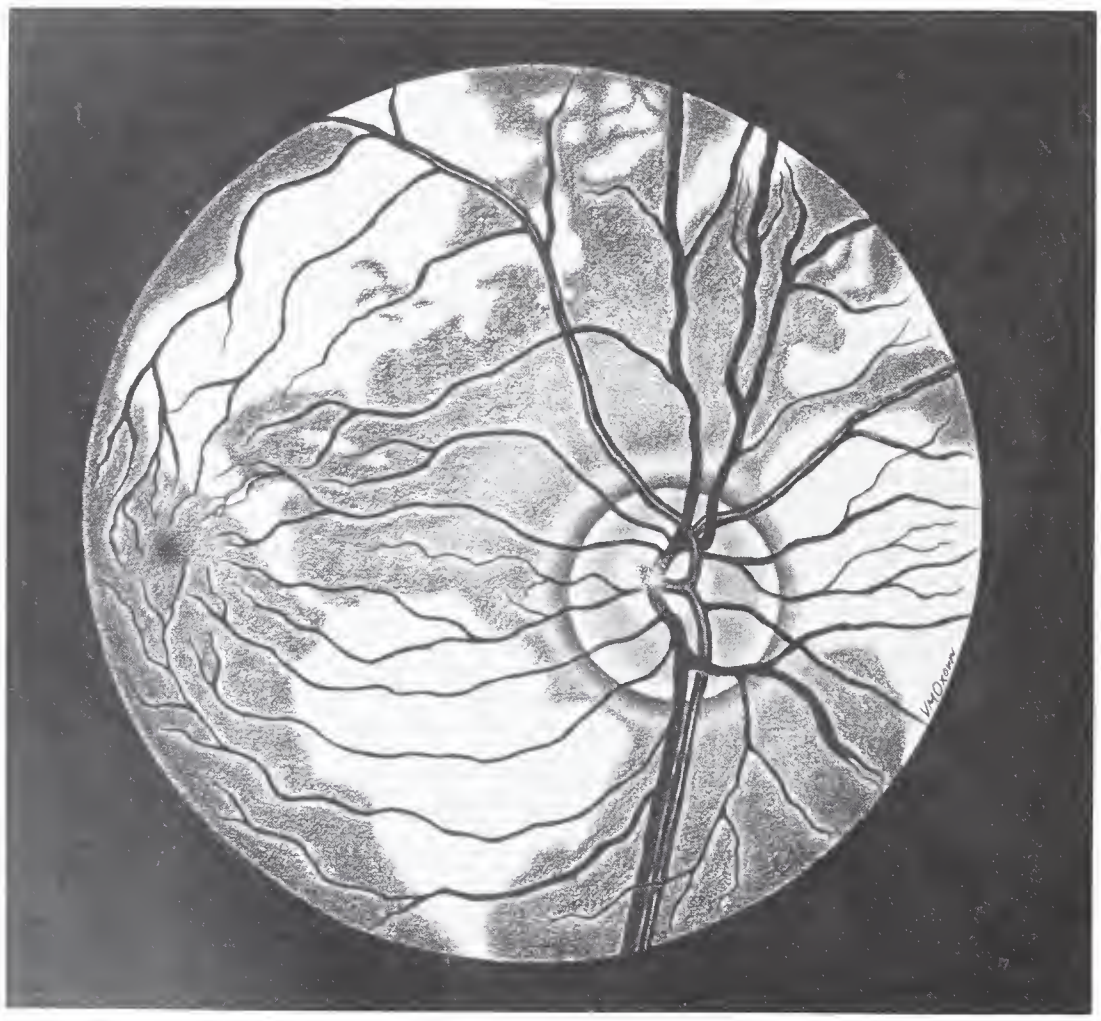
*Faculty Member, Department of Ophthalmology, University of Toronto; Attending Ophthalmologist, Toronto Hospital, General Division

Abstract

Cytomegalovirus (CMV) retinitis is the most common ocular opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS). It usually develops in the late stages of the syndrome when patients are the most severely immunocompromised. CMV retinitis is a necrotizing infectious retinitis with a characteristic funduscopic appearance. It results in severe visual loss and blindness if left untreated. Retinitis and chorioretinitis can also be caused by *Toxoplasma gondii*, herpes simplex virus, varicella-zoster virus, *Treponema pallidum*, *Pneumocystis carinii*, and *Candida albicans*, among other organisms. The differential diagnosis of retinitis is aided by characteristic features of CMV retinitis and other AIDS-related retinopathies. Induction treatment followed by maintenance therapy with ganciclovir or foscarnet has been found to stabilize CMV retinitis and to slow its progression. In studies comparing foscarnet and ganciclovir, foscarnet was found to be as effective as ganciclovir in the treatment of CMV retinitis. The prevalence of human immunodeficiency virus - type 1 (HIV-1), combined with the prolonged lifespan of AIDS patients, necessitates the important introduction of screening programmes to identify early CMV retinitis in AIDS patients.

Introduction

Cytomegalovirus (CMV) is an enveloped herpesvirus consisting of an icosahedral capsid and a double-stranded DNA core. The virus infects the majority of the population at some time in their life and it is estimated that at least 80-85% of adults are infected by age 40. It establishes latent infections in epithelial cells throughout the body. Present in urine, stool, saliva and other excretions, the virus can be transmitted by intimate contact with individuals shedding the virus. Sexual contact, intrauterine or perinatal exposure, breast milk, blood transfusion, and organ transplants are additional modes of transmission[1,2]. CMV infection of the immunocompetent individual is usually benign and asymptomatic[2].



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CMV infection in persons with AIDS is felt to result from reactivation of latent infection[3]. Once the virus is reactivated, it is capable of disseminating throughout the entire body as cell-mediated immunity is decreased and the patient is unable to control the infection. CMV is the most common opportunistic pathogen found on autopsy of AIDS patients[4]. In about 30% of AIDS patients CMV is recognized as a major contributor to death[4]. Other systemic effects of CMV infection besides retinitis are enteritis and pneumonitis. CMV has also been reported to cause cerebral disease, myelitis, pericarditis, glomerulonephritis, hepatitis, and adrenal necrosis[4,5]. Basically,

CMV has been reported to affect virtually every organ system. However, the precise contribution of CMV disease to the clinical course of late-stage HIV infection remains undefined[6].

Cytomegalovirus retinitis is the most common ocular opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS). Prior to the AIDS epidemic, CMV retinopathy was an uncommon disorder, seen primarily in transplant recipients and persons receiving immunosuppressive therapy[3]. Now, as many as 15% to 46% of AIDS patients develop CMV retinitis[1,7,8]; the variation in prevalence results from studies having been done on different patient populations. The prevalence may be increasing as severely immunocompromised patients are surviving longer due to the use of prophylactic treatment against opportunistic diseases[7]. When untreated, CMV retinitis is a relentlessly progressive disease. Once involvement of the optic nerve or macula has occurred, blindness results[9,10]. In order to increase chances of maintaining functional eyesight for the patient, early detection and prompt institution of appropriate antiviral therapy are necessary[9]. In order to carry out this objective, the combined efforts of internists and ophthalmologists are required.

Natural History

CMV infection of healthy individuals rarely leads to ocular involvement. In contrast, it represents a virulent opportunistic pathogen in immunocompromised patients such as AIDS patients[1]. CMV retinitis is typically a late manifestation of AIDS and is associated with severe CD4+ lymphocyte depletion[11,12]. Studies have shown that there is a 30-40% increased risk of the development of CMV retinitis when the CD4+ cell count is less than 50 cells/mm^3 [9,11,12]. It has also been shown that manifestation of a prior AIDS-defining illness is associated with an increased risk of progression to CMV retinitis[11].

CMV retinitis is observed much more frequently in North America than in Africa[3]. The reasons for this disparity are not known. One possibility is that the cases of CMV retinitis in Africa are under-recorded. Another factor may be related to patient mortality which is higher in Africa, perhaps due to the lack of anti-retroviral and prophylactic

Figure 1: Funduscopic Presentations of CMV Retinitis

Figure 1a: Posterior pole

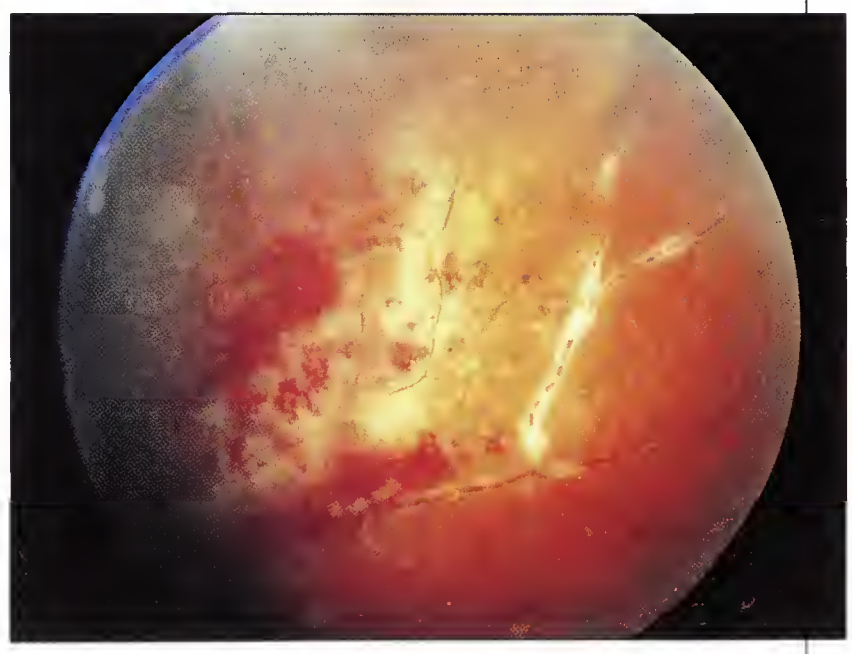

Figure 1b: Periphery

Figure 1c: Optic disc

Figure 1d: Slowly sclerosing retinitis in periphery

therapy available in the region. Thus in Africa, AIDS patients may simply be dying before they are sufficiently immunocompromised to develop CMV[13].

CMV retinitis usually presents unilaterally, although as many as 35% of patients will have developed bilateral disease at presentation. If left untreated, unilateral infection will progress to involve the other eye, presumably by random hematogenous spread of the disseminated infection[1,9].

Patients with CMV retinitis have disseminated disease and they presumably die of CMV infections in other organs such as the lungs and the gut. Therapy with ganciclovir or foscarnet treats the disseminated disease as well as the retinitis allowing patients with CMV infection to live longer. At the time when AIDS was a newly discovered disorder, the median survival of untreated CMV retinitis patients was about four months from the time of ophthalmic diagnosis[14]. Recently, the median survival has been reported to be between 8.5 and 12.6 months[15]. This increase may stem from earlier diagnosis and improved treatment of CMV retinitis[3,15].

Clinical Features

CMV retinitis is characterized by a progressive necrotizing retinitis. Active lesions are white and granular and are frequently associated with hemorrhage and mild vitreal inflammation. Some authors describe this condition as "cottage cheese with ketchup" retinopathy[1].

Four different funduscopic presentations of CMV retinitis have been observed. Over fifty percent of cases present with a dense, white area of retinal necrosis at the posterior pole associated with areas of retinal hemorrhage (Figure 1a). Infection can also begin in the periphery (Figure 1b) or at the optic disc (Figure 1c), causing white lesions with associated hemorrhage at these sites. A rare presentation is a slowly creeping sclerosing retinitis that begins at the periphery. This type does not demonstrate any signs of active disease such as exudates and hemorrhage and only shows advanced retinal atrophy (Figure 1d).

Retinal involvement usually follows a vascular distribution, producing large areas of necrosis with smaller perivascular infiltrates. The advancing edge of these lesions is usually very sharp and has irregular margins. Typically, over several weeks, untreated lesions progress to full-thickness necrosis with retinal gliosis. The pathway of the expanding lesion can be predicted by the presence of venous sheathing or white dots at the leading edge indicative of direct cell-to-cell infection. Expanding lesions often acquire a brushfire border[1,9]. Resolution of full-thickness retinal necrosis and retinal pigment epithelial necrosis leaves atrophic and avascular zones with areas of pigment dispersion[14]. CMV lesions usually progress slowly, but the time required for lesions to double in size can vary enormously from one week to two months. Most untreated cases of unilateral infection will progress to involve the other eye in four to six weeks.

In contrast to other opportunistic infections of the retina, CMV retinitis is rarely accompanied by vitritis and iritis. If vitritis and iritis do occur, they are associated with fine, non-granulomatous keratotic precipitates on the corneal epithelium[14,16].

The clinical signs and symptoms of CMV retinitis include blurring of vision, blind spots, and floaters. Pain and redness do not develop[3]. With involvement limited to the peripheral retina, patients either have no complaints or may complain of floaters. If the retinitis begins at the posterior pole, the patient may complain of a visual field deficit. The possible causes of visual loss are direct retinal necrosis by infection, optic nerve involvement, and retinal detachment[1].

Retinal detachment occurs in some cases of treated and untreated CMV retinitis[1,17]. The detachment can be either serous or rhegmatogenous (tear-induced), although the latter is much more common. Rhegmatogenous retinal detachment may occur during the active or inactive phases of the disease. These detachments are difficult to repair because of the markedly fragile nature of the atrophic retinal tissue. However, many cases can be repaired successfully with the use of silicone oil, which provides a long-acting tamponade to the areas of atrophic retina[18].

Histopathology

Gross specimen studies reveal extensive areas of necrosis, often extending from the posterior pole to the periphery[14]. This full-thickness necrosis produces white, edematous, granular zones of retinitis[9].

Histological sections show diffuse full-thickness necrosis of the retina as well as necrosis of retinal pigment epithelium. Enlarged CMV-infected cells with basophilic intranuclear and intracytoplasmic inclusions are present[9]. Some of the cells exhibit the typical owl's eye appearance characteristic of CMV infection. Usually there is a sharp demarcation between CMV-infected and normal areas of the retina, but the borders are often irregular[1,14]. CMV primarily infects the neurosensory retina, although atrophy of the retinal pigment epithelium and non-granulomatous inflammation of the choroid may also be observed[9,16]. Typically, in active disease, a neutrophilic rather than lymphocytic response is observed, reflecting the mononuclear cell depression[14]. Inactive atrophic lesions are associated with minimal or absent ocular inflammation[1,14]. Vascular findings commonly associated with CMV infection of the retina include retinal edema, perivasculitis, arteriolar attenuation, and venous occlusion[9,16,17]. CMV infection of the optic nerve causes intense swelling, papillitis, and necrosis[1].

Electron microscopy may reveal necrotic retinal cells, some of which contain virus particles similar in size and shape to those from the herpesvirus family. These particles may be seen both in the nucleus and in the cytoplasm of infected cells[1].

Differential Diagnosis

Cotton-wool spots

Although CMV retinitis is the most common ocular opportunistic infection associated with AIDS, it is not the most common ocular finding. The most common ocular lesions in AIDS are cotton-wool spots which appear in more than 50% of AIDS patients, although the incidence may be as high as 71% as suggested by autopsy studies[3,9,14]. Various causes have been hypothesized, including damage caused to the endothelial cells by direct HIV infection, deposition of immune complexes, and alterations in blood flow. The spots appear as white, fluffy infiltrates at the posterior pole and are in the superficial layer of the retina, unlike CMV retinitis which has a characteristic granular appearance and lies much deeper within the retina[9]. The cotton-wool spots seen in persons with AIDS represent focal areas of swelling of the nerve fiber layer in response to retinal ischemia associated with microvasculopathy of the retina[3,12]. Cotton-wool spots are not associated with gross visual disturbances. They resolve in 4-6 weeks without any treatment and leave no clinical trace. However, new lesions may develop as old ones resolve[14].

The differential diagnosis of CMV retinitis includes other viral retinopathies, such as herpes simplex virus and varicella-zoster virus; the acute retinal necrosis syndrome; toxoplasmic retinochoroiditis; Candida retinitis; *Pneumocystis carinii* infection; and ocular syphilis[1,19].

Figure 2: Acute retinal necrosis

Herpes simplex virus

Herpes simplex virus produces a smooth white retinitis associated with perivenous sheathing and retinal edema. Hemorrhage is rarely present. Most cases of herpes simplex virus retinitis can be diagnosed clinically[1,6]. However, in cases resembling CMV retinitis, an anterior chamber paracentesis can be performed and the aqueous cultured and tested to confirm the diagnosis[20].

Varicella-zoster virus

Varicella-zoster virus (VZV) retinitis is rapidly progressive[1,3,6]. However, in contrast to CMV retinitis, it is less aggressive. VZV retinitis is a diffuse exudative necrotizing retinitis which is mottled in appearance and is occasionally associated with hemorrhage. It usually occurs peripherally with possible macular extension. It is not uncommon for herpes zoster to affect the ophthalmic branch of the trigeminal nerve, causing herpes zoster ophthalmicus[1]. Diagnosis is made clinically, but if difficult, it can be confirmed by cultures of aqueous fluid[20].

Acute retinal necrosis syndrome

Acute retinal necrosis (ARN) is caused in the majority of cases by herpes zoster and less commonly by herpes simplex. Many patients with acute retinal necrosis have had a dermatomal herpes zoster infection in the preceding months. The classic presentation is characterized by severe peripheral retinal vascular occlusion overlying a white necrotic retina. The progressing necrosis of the retina appears as a white wall beginning in the periphery and rapidly moving towards the posterior pole (Figure 2). A sharp demarcation between the area of involvement and the normal retina is present. Both the location and the sharpness of the demarcation line help differentiate the disorder from CMV retinitis. A prominent feature of ARN is severe vitritis. Differentiation of CMV retinitis from ARN may be based on the rapid progression and the presence of severe vascular compromise in the latter[1,19].

Ocular toxoplasmosis

Although the prevalence of ocular toxoplasmosis in HIV-positive patients is only 3%, it is the second most common cause of retinal infection in AIDS patients. The

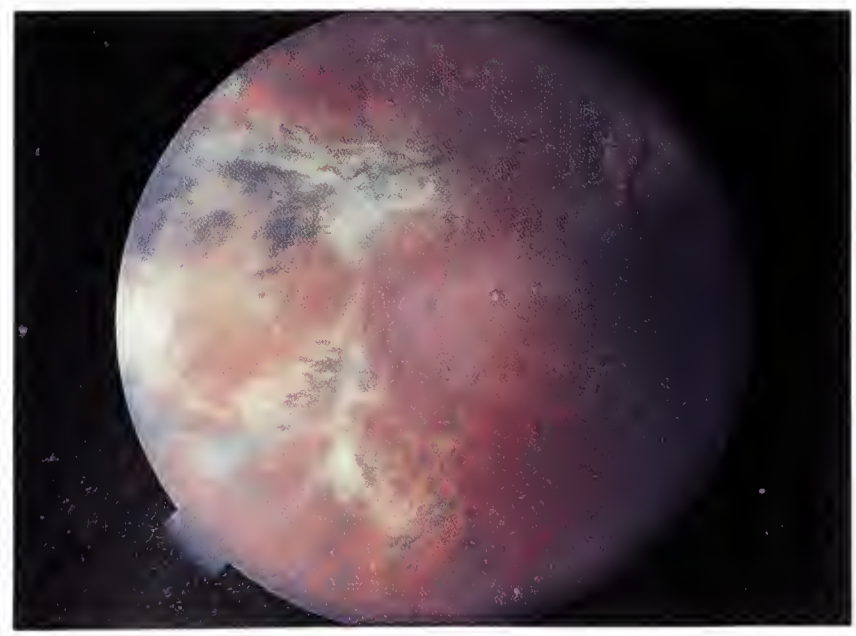

Figure 3: Ocular toxoplasmosis

diagnosis is based on clinical criteria. The main difference distinguishing ocular toxoplasmosis from CMV retinitis is the severe inflammation of the vitreous and aqueous seen in ocular toxoplasmosis. The retinal necrotic areas are also different from CMV lesions in that they are more fluffy and edematous, are generally non-hemorrhagic, and have hazy edges. Most toxoplasmic retinal lesions in AIDS are unifocal and are located in the posterior pole. The lesions have irregular margins and are associated with an old pigmented, irregular scar of the retinochoroid layer (Figure 3)[1,21].

In AIDS patients, ocular toxoplasmosis is often associated with cerebral toxoplasmosis[10]. Cerebral computed tomography (CT) is therefore mandatory when ocular toxoplasmosis is diagnosed in order to rule out CNS involvement. In addition, funduscopy is mandatory when cerebral toxoplasmosis is diagnosed[21].

Candida and other fungal infections

Necrotizing retinitis caused by *Candida albicans* and other fungi such as cryptococcus is characterized by single and sometimes multiple fluffy white exudative retinal lesions. In later stages, vitreous extension may occur. Fungal infections of the retina are very characteristic and should not be considered part of the differential for CMV retinitis[19].

Syphilis

Acquired syphilis can cause a focal or diffuse retinitis, and patients may be co-infected with both *Treponema pallidum* and CMV[9]. The ocular findings can be quite varied, although the majority of the patients present with neuroretinitis or optic perineuritis. Two thirds of patients have laboratory evidence of concomitant neurological involvement, with about one third showing signs of acute meningitis[19]. Serology for syphilis usually reveals the diagnosis. Generally, a VDRL test is used for screening, while a fluorescent treponemal antigen absorption (FTA-ABS) or microagglutination assay for *Treponema pallidum* (MHA-TP) is used as a confirmatory test[14]. Although both syphilitic and CMV infections produce a necrotizing retinitis, the former frequently is accompanied by an inflammatory reaction of the vitreous.

Pneumocystis carinii choroiditis

Pneumocystis carinii pneumonia is estimated to occur in approximately 60% of all AIDS patients; fewer than 1% of these will have extrapulmonary pneumocystosis[22]. *P. carinii* choroiditis represents 4% of these extrapulmonary pneumocystoses[22]. *P. carinii* choroiditis consists of numerous slightly elevated, plaque-like, yellowish-white choroidal lesions deep to the retina, predominantly in the posterior pole with minimal associated inflammation. These lesions neither involve the retina nor are associated with hemorrhages and thus should not be confused with CMV retinitis. The infection begins with small discrete lesions that progressively enlarge and coalesce. A history of *P. carinii* pneumonia is an additional factor suggestive of *P. carinii* choroiditis. As with syphilis, *Pneumocystis carinii* choroiditis and CMV retinitis may be present concurrently[19,22].

In addition to the above differential diagnoses, concurrent multiple retinal and choroidal infections must be considered. Frequent superinfection with multiple organisms including CMV has been documented in AIDS patients, and may include herpes simplex virus, *Candida albicans, Toxoplasma gondii,* various *Mycobacteria spp., Pneumocystis carinii, Cryptococcus neoformans* and various bacteria[1]. Infection of the retina by two of these organisms is common and infection by three organisms is not unknown.

Figure 4: CMV Retinitis

Figure 4a: Before treatment

Figure 4b: After treatment with ganciclovir

Definitive Diagnosis

The diagnosis of retinitis in AIDS patients is based on a number of factors including ophthalmic appearance, underlying disease, clinical history and severity of underlying immunocompromised state, systemic physical findings, and laboratory studies. CMV is by far the most common causative organism, with CMV retinitis representing at least 95-98% of cases of retinitis in AIDS patients[19]. In most cases, the uncommon AIDS-related retinopathies are characteristic in their appearance and can easily be differentiated from CMV retinitis by an experienced ophthalmologist. In the presence of suspicious, mixed, or atypical findings, serum laboratory tests such as complement fixation, immunofluorescence, and ELISA techniques can be used for confirmation[1,10].

Polymerase chain reaction (PCR), which amplifies a DNA sequence, can be used to increase the speed of diagnosis of CMV retinitis and to improve prediction of the efficacy of antiviral therapy. Persistently high PCR levels of cytomegalovirus DNA always precede virus isolation and may be the first indication of organ involvement, thus allowing early treatment[23].

Cytomegalovirus, herpes simplex virus, and varicella-zoster virus particles have been detected in aqueous humour[1,20]. Anterior chamber paracentesis can be performed to detect these antigens and their antibodies in samples of the aqueous humour. However, these tests require substantial amounts of aqueous humour (25-200 µl)[20].

Rapid and accurate diagnosis is essential in preserving visual function since some forms of retinitis are rapidly progressive and appropriate treatment varies with the diagnosis[9,19].

Treatment

Therapy of CMV retinitis needs to be initiated as soon as possible because if left untreated the retinal lesions will progressively enlarge and result in marked visual loss and eventual blindness[1]. Treatment is instituted to delay progression of disease, to stop involvement of the possibly uninfected other eye and to preserve visual acuity[9]. In order to assess treatment of CMV retinitis, the disease is defined as either active or inactive. Active lesions are those with retinal edema, necrosis at the borders, and hemorrhage. Inactive lesions are those with atrophic and gliotic retinal scarring and resolution of the previously edematous and necrotic borders[10] (Figure 4).

The two drugs presently available for the treatment of CMV retinitis are ganciclovir and foscarnet.

1. Ganciclovir

Ganciclovir (DHPG) is a synthetic nucleoside analogue of 2' deoxyguanosine that inhibits replication of all herpesviruses. It accomplishes this by competitively inhibiting viral DNA polymerase after intracellular triphosphorylation and by directly incorporating itself into viral DNA. The result is the termination of DNA elongation[1,8,10,24]. Ganciclovir is virastatic. Hence, since the virus is not eliminated from the eye, retinitis will recur if treatment is terminated[1,8,24]. Thus, maintenance doses at regular intervals are a critical factor in treatment.

The recommended induction dose of ganciclovir is 5 mg/kg intravenously over one hour every 12 hours for 14-21 days. After induction therapy is completed, the recommended maintenance dose is 5 mg/kg IV over one hour once per day seven days a week for life. Patients are capable of self-administering IV ganciclovir therapy following instruction from a nurse[5]. Many patients may experience breakthrough reactivation requiring administration of an additional induction course. The incidence of breakthrough retinitis appears to range between 30 and 50%. Most studies demonstrate improvement or stabilization of vision in over 80% of patients[1,8,25]. Monthly assessment of treatment efficacy is recommended.

The most common side effects of ganciclovir include neutropenia and thrombocytopenia, making neutrophil and platelet counts important. Medication should be withheld if neutrophil count falls below 500 cells/ mm^3. Other side effects include fever, rash, anemia, and abnormal liver function tests[1].

Zidovudine (AZT), a drug with activity against HIV, prolongs survival of patients with AIDS and decreases the number of opportunistic infections. Unfortunately, this anti-retroviral drug cannot be given concurrently with ganciclovir because of increased risk of neutropenia when the two drugs are given simultaneously[1,10,25].

Hematologic toxicity is the primary dose-limiting factor. In an effort to find possible alternatives for patients with refractory CMV retinitis or those who develop severe neutropenia, combination therapy consisting of intravenous ganciclovir and granulocyte-monocyte colony-stimulating factor (GM-CSF) or ganciclovir combined with CMV hyperimmune globulin is being evaluated[1].

Another interesting alternative that has produced favourable results is intravitreal injection of ganciclovir[26,27]. The advantages include eliminating the need for hospitalization, avoiding catheter-associated septic risks of IV infusion, and reducing the myelosuppressive effect of systemic ganciclovir, which enables the patient to remain on concomitant zidovudine therapy. The disadvantages include the loss of beneficial systemic effects of ganciclovir against disseminated CMV infection and the logistical difficulties associated with performing intraocular injections twice weekly for the patient's remaining lifetime. Potential complications include retinal detachment, vitreous hemorrhage, and endophthalmitis. The primary indications for intravitreal therapy include severe neutropenia precluding the use of systemic ganciclovir, and vision-threatening lesions of the macula and optic nerve[1,27,28]. Recently, a surgically implanted device for sustained intravitreal release of ganciclovir has been developed[1,28].

2. Foscarnet

Foscarnet is a pyrophosphate analogue which exerts its antiviral activity by selective inhibition of all herpesvirus DNA polymerase at concentrations that do not affect cellular DNA polymerases[1]. This drug also inhibits the reverse transcriptase of HIV-1[1,25].

The recommended induction therapy is 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours for 2 weeks. This is followed by a maintenance dose of 90 mg/kg daily[1,5,25]. Intravenous foscarnet therapy can be self-administered. Like ganciclovir, foscarnet is virastatic and reactivation occurs when the drug is discontinued. While neutropenia is the major side effect of ganciclovir, nephrotoxicity is the dose-limiting side effect of foscarnet. Thus, regular serum creatinine measurements are required. Other side effects include infusion site thrombophlebitis, decrease in hemoglobin, increase or decrease in serum calcium levels, lethargy, irritability, tremor, headache, seizure, and status epilepticus[1,9,25]. Zidovudine can routinely be given with foscarnet without the occurrence of increased toxicity resulting from either agent[1,25].

In studies comparing foscarnet and ganciclovir, foscarnet was found to be as effective as ganciclovir in the treatment of CMV retinitis. Recently, a randomized study from the Studies of the Ocular Complications of AIDS demonstrated increased survival from the time of diagnosis of CMV retinitis in patients with AIDS who were initially randomized to receive IV foscarnet (12.6 months) compared with those patients initially randomized to receive IV ganciclovir (8.5 months)[15,26]. There are several possible explanations for the observed increase in survival. Treatment with foscarnet may control the systemic CMV infections which may be contributing to mortality in persons with AIDS. The compatibility of foscarnet with zidovudine allows patients to receive this anti-retroviral therapy, whereas ganciclovir is relatively incompatible with zidovudine. Finally, as demonstrated by decreasing circulating HIV p24 antigen levels both when the drug is used with zidovudine and alone, foscarnet has marked intrinsic anti-retroviral activity[1,25].

CMV retinitis in AIDS patients is best managed by a team of physicians. The patient's overall status and management with antiviral drugs are best assessed by an internist familiar with the drug side effects, while diagnosis of retinal disease and monitoring of the response of the patient's retinopathy to treatment is best done by an ophthalmologist. The choice between ganciclovir and foscarnet for initiation of treatment for CMV retinitis should be left to the patient and his or her physician. The decision is based on patient tolerance to the drug with regard to side effects[3,9]. Some investigators suggest that foscarnet should become the initial treatment of choice for CMV retinitis in persons with AIDS because of its intrinsic anti-retroviral activity and data suggesting that it may prolong survival in persons with HIV infection and CMV retinitis. However, in one study, 42% of the patients required change to ganciclovir therapy at some time after their initial foscarnet treatment because of renal insufficiency and progressive retinal disease[25]. In practice, ganciclovir is still the initial choice for treatment because of the convenience of its use[7]. Ganciclovir infusion takes one hour, while foscarnet infusion takes three hours due to the larger volume of saline which is administered initially to reduce nephrotoxicity. However, foscarnet remains an important therapeutic alternative to ganciclovir therapy for CMV infections and for other viral infections that may be resistant to standard therapies[25].

These drugs are effective but associated toxicities limit the effectiveness of treatment. Studies currently are under way to determine whether alternating or combining reduced-dose regimens of ganciclovir and foscarnet can lower the incidence of dose-limiting side effects while potentially enhancing therapeutic outcome through additive or synergistic interaction of the agents[29].

Screening & Prevention

Screening programmes to identify AIDS patients with early CMV retinopathy and other ophthalmic problems are needed. The fact that CMV retinitis and other HIV-related retinal problems demonstrate an increased risk for patients with low CD4+ count provides a basis for screening strategies and chemoprophylaxis[12]. Monitoring CD4+ cell count regularly is an integral part of this strategy. Current recommendations include screening patients with AIDS or CD4+ lymphocyte counts $\leq$ 200 cells/mm^3 every 2-3 months[11]. Funduscopic screening should be carried out by the patient's primary health care provider[5]. However, given the increasing number of patients with HIV infection, frequent screening of all patients may be unrealistic. With the issue of limited health care resources in mind, many researchers have suggested that patient education be a crucial component in early detection of CMV retinitis in AIDS patients. Infected individuals and their primary care providers should be made familiar with clinical signs and symptoms of CMV retinitis and encouraged to seek ophthalmic examination at any sign of such symptoms. As the length of AIDS patients' survival increases, quality of life issues become more and more important. Preservation of sight is very important to AIDS patients and ophthalmic examination greatly increases their well being. Studies currently under way involve the development of an orally administered drug to be used in the prophylaxis of AIDS-related ophthalmic disease.

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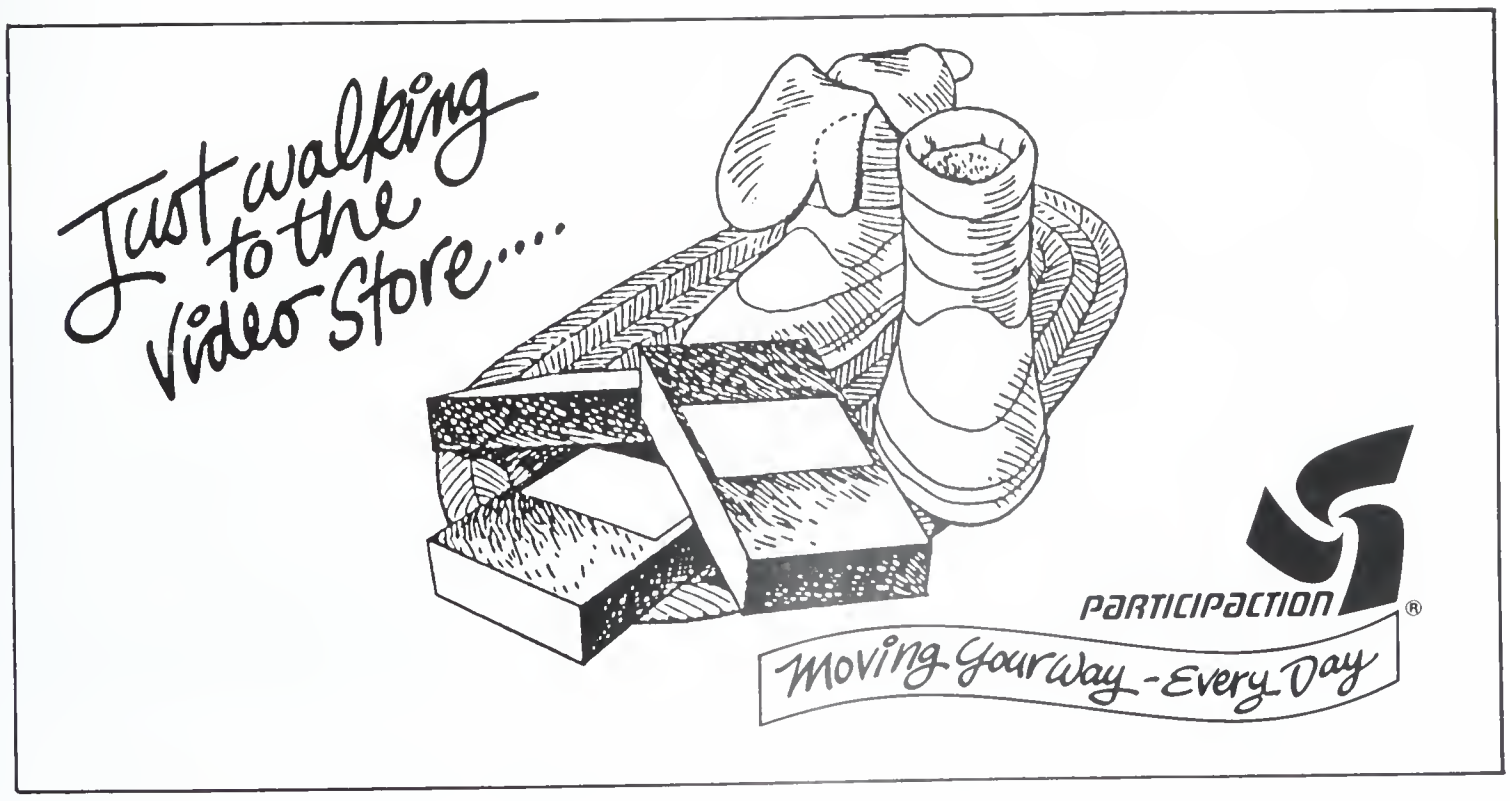


Perspectives on Interventional Cardiology and Advances in Invasive Methods

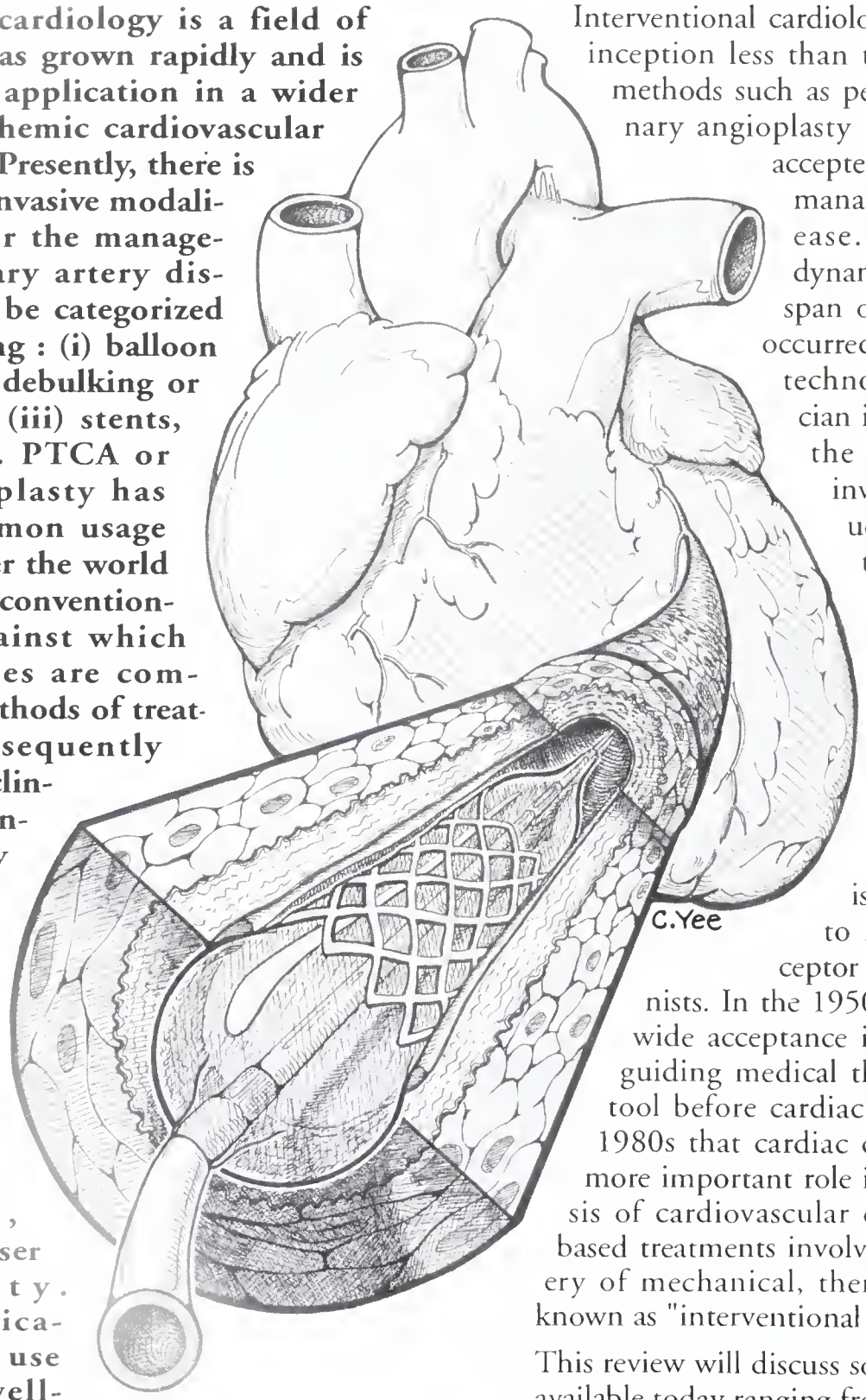
Douglas Lee (9T4) and Leonard Schwartz*, M.D., F.R.C.P.(C)

*Associate Professor of Medicine, University of Toronto

Abstract

Interventional cardiology is a field of medicine that has grown rapidly and is finding greater application in a wider spectrum of ischemic cardiovascular disease settings. Presently, there is a wide array of invasive modalities available for the management of coronary artery disease. These can be categorized into the following : (i) balloon angioplasty, (ii) debulking or tissue removal, (iii) stents, and (iv) lasers. PTCA or balloon angioplasty has come into common usage in centres all over the world and remains the conventional standard against which other modalities are compared. Other methods of treatment have subsequently been subject to clinical or experimental use and may become widely accepted and utilized in the near future. These methods include directional coronary atherectomy (DCA), rotablation, stenting, and laser angioplasty. Although indications for their use are not as well-defined as they are for PTCA, each modality has particular advantages and disadvantages which may clarify its role in the treatment of ischemic heart disease.

Introduction



Interventional cardiology has grown rapidly since its inception less than two decades ago and invasive methods such as percutaneous transluminal coronary angioplasty (PTCA) have become widely accepted and routinely utilized in the management of ischemic heart disease. The field of cardiology is dynamic and in this relatively short span of time, further advances have occurred with the advent of innovative technologies. The practising physician in future decades will likely see the rise or fall of some of these invasive modalities as we continue to make greater inroads into the treatment of coronary artery disease.

The first description of the clinical effectiveness of nitrates (amyl nitrate) in angina pectoris was by Brunton in 1867. With time, the pharmacologic armamentarium to manage ischemic heart disease increased to include nitrates, beta-adrenoceptor blockers, and calcium antagonists. In the 1950s, cardiac catherization gained wide acceptance in evaluating disease states, in guiding medical therapy and as a pre-operative tool before cardiac surgical repair. It was in the 1980s that cardiac catherization began to play a more important role in treatment as well as diagnosis of cardiovascular disease. These catherization-based treatments involving microsurgery or the delivery of mechanical, thermal or light energy became known as "interventional cardiology"[1].

This review will discuss some of the invasive technology available today ranging from the tried and accepted conservative standards to the more technologically advanced and experimental techniques which may be in common usage in the future. At present, there are four major categories of interventional cardiologic

approaches to the treatment of coronary artery disease : (i) balloon angioplasty; (ii) debulking methods and tissue removal (e.g. atherectomy and rotational ablation); (iii) intravascular stents; (iv) lasers. Each of the above present particular advantages and disadvantages and all may eventually find a place in the management of myocardial ischemia.

I. Balloon Angioplasty

The introduction of percutaneous transluminal coronary angioplasty (PTCA) occurred only 16 years ago. Since that time, there have been a number of new advances and developments and a wider acceptance of PTCA in various clinical applications with more complex coronary vessel disease (Figures 1 and 2). However, restenosis, the re-narrowing at the treated site, has dogged the success of PTCA and as yet, no practical therapeutic solution is available.

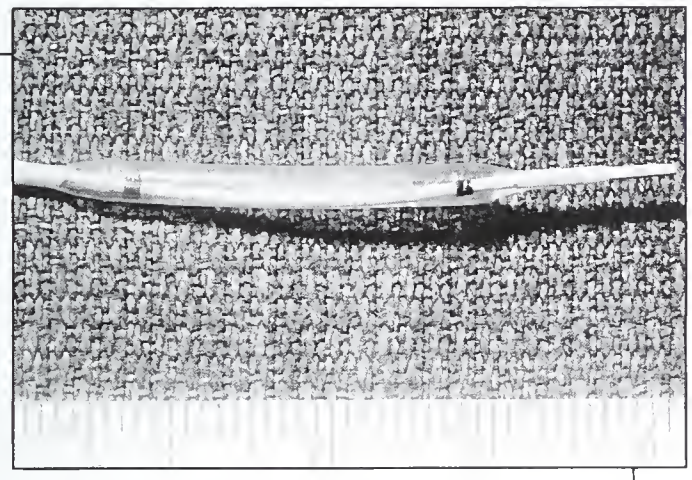


Figure 1: PTCA angioplasty balloon catheter.

The mechanism of coronary angioplasty was initially believed to be the result of plaque compression[2]. It is now generally accepted, however, that lumenal widening is secondary to fracture of the plaque and its subsequent untethering, making it susceptible to stretch[3,4]. This has been demonstrated in post-mortem studies[5,6] and by intravascular ultrasound[7].

The success of PTCA relates to multiple factors including operator experience and skill, appropriate case selection, and angiographic evaluation before and after angioplasty. High-quality angiography and digital video playback play a crucial role at all stages of the invasive intervention. Case selection is based on lesion assessment at angiography by the criteria of lesion morphology, branching, extent of coronary disease, and left ventricular function[8]. Intra-procedural and post-procedural angiographic assessment are important in the determination of the resultant lesion morphology, branch anatomy, distal runoff, efficacy of lesion dilatation, and restenosis. When one considers that coronary flow is proportional to lumen radius raised to the fourth power, one can appreciate that small changes in estimates of internal diameter may have great implications in terms of coronary flow reserve[9]. Thus, angiographic accuracy is important in the achievement of good outcomes after invasive procedures. With the advent of new techniques to visualize intracoronary anatomy (e.g. intracoronary ultrasound) there may be further improvements in outcome.

At present, PTCA has found a broader range of application in selected patients with multivessel disease, acute and subacute total occlusions, complex branch disease, post-coronary artery bypass graft surgery, and post-cardiac transplantation. Great interest has arisen in the prospects for angioplasty to counteract ischemic left ventricular dysfunction in stunned or hibernating myocardium and in unstable angina[8]. Angioplasty has been shown to be superior to medical therapy in the treatment of single vessel disease in a randomized trial (Angioplasty Compared with Medicine or ACME), with fewer anginal attacks in follow-up and a better treadmill performance (greater total exercise time, maximal heart rate - blood pressure product and duration of angina-free exercise)[10].

The utility of immediate angioplasty in patients with acute myocardial infarctions has been under recent examination[11-13]. These studies have compared immediate

Figure 2: Balloon angioplasty. Angiograms taken before, during, and after balloon dilatation.

angioplasty with the standard thrombolytic therapy and it was shown that the former may produce a better outcome than the latter. Thrombolytic therapy has a number of drawbacks including failure to produce arterial patency (20% of cases)[14-16], bleeding complications[17], recurrent ischemia, and hemorrhagic infarction[18-20]. Immediate PTCA was found to be associated with greater early patency of the infarct-related artery (rates exceeding 90%) and a less severe residual stenosis than with thrombolysis[11,12], with decreased rates of bleeding complications (e.g. intracranial hemorrhage). In addition, LV function was better than or comparable to that following thrombolysis with less recurrent myocardial ischemia, reinfarction and death[11,12]. It appears that with improvement in technical skills, catheter technology, and case selection, immediate PTCA may show further benefit above and beyond that of thrombolysis alone. Other factors, including the importance of aspirin[19,21] and adequate anticoagulation during angioplasty[22], may also improve outcomes after PTCA. The logistics of PTCA in evolving myocardial infarction are important. In Canada, with relatively inaccessible tertiary centres, the delay is usually too great.

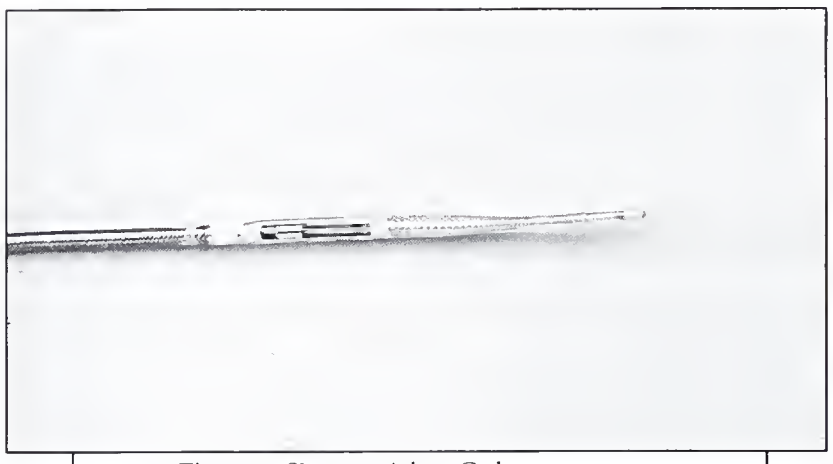


Figure 3: Simpson AtheroCath.

The major obstacle to the success of angioplasty and almost all invasive procedures to date is restenosis, which is generally defined as a 50% or greater diameter stenosis at the PTCA site at follow-up angiography. Restenosis occurs in 35-50% of cases, usually within the first six months after the procedure. This has been a very active area of research in the clinical and basic sciences. Some commonly accepted risk factors for restenosis have been identified using quantitative coronary angiography. These include lesions of a proximal left anterior descending coronary artery[23,24], total occlusion prior to PTCA[25], presence of collateral vessels supplying the distal aspect of the dilated coronary artery[26,27], incomplete dilatation, and a residual pressure gradient[23,28]. Re-narrowing secondary to intimal hyperplasia is a generalized reaction of the vascular wall to injury and occurs in most although not all cases. The more the initial gain, the greater the amount of re-narrowing, but the latter does not match the former and the clinical and angiographic outcome is better with a better initial result[29-31].

There have been other innovations in angioplasty techniques which may have a positive impact on the success of PTCA. Adjunctive thrombolytic therapy has been described in recanalizing occluded coronary bypass grafts[32], in native coronary arteries with subtotal or total occlusions[33], and in salvaging failed angioplasties (abrupt occlusions) secondary to arterial thrombosis[33]. Prolonged infusions of intracoronary urokinase (i.e. 18 to 24 hours) followed by definitive balloon angioplasty of the graft has been suggested for patients with refractory angina who are not candidates for repeat bypass surgery. Additionally, abrupt occlusions may not necessarily have to go to emergency bypass surgery if thrombolysis is successful.

Prolonged balloon inflations are now possible with newly developed perfusion balloon catheters which allow distal flow of blood through the guidewire lumen of the catheter and 5 to 15 minute balloon inflations have been performed. It is believed that longer balloon inflations may help overcome elastic recoil of dilated arteries and may be of use in the treatment of flaps or dissections (abrupt occlusions) caused by balloon inflation[33].

Finally, the future may hold a variety of novel support devices which may be applicable in high risk or complicated PTCA[34]. These cases would likely be situations where even transient coronary occlusion with balloon inflations would be too great of an ischemic burden, leading to decompensation and hemodynamic collapse. There may also be situations where ischemia is refractory to medical therapy in patients who are not candidates for coronary bypass surgery (i.e. markedly reduced LV function, unfavourable target vessels or non-cardiac contraindications) and thus percutaneous procedures may be the only viable therapeutic option. These support devices include intra-aortic balloon counterpulsation, anterograde active transcatheter coronary perfusion, coronary sinus retroperfusion, cardiopulmonary bypass, Hemopump left ventricular assistance and partial left heart bypass.

II. Atherectomy & Rotational Ablation

The Simpson AtheroCath is used widely as a device to remove atheromatous plaque. It consists of a cylindric housing with a balloon on one side which is inflated to less than one atmosphere of pressure to position the cutting blade against the plaque. A motorized cutter rotating at 2500 rpm located inside the housing cuts the plaque which is then packed into the distal nose cone (Figure 3).

The mechanisms of coronary lumen enlargement by directional coronary atherectomy (DCA) are likely multiple. Debulking has been described to be one mechanism (Figures 4a and 4b). Interestingly, the excision of plaque material as the lone mechanism is insuf-

ficient to account for the angiographic improvement observed with DCA[35]. Thus, impedance to elastic recoil and the balloon dilatation itself have been postulated to stabilize and dilate the arterial wall ("facilitated angioplasty")[36]. The device itself is large and inflexible and thus its use has been limited to short eccentric stenoses in proximal and middle portions of non-tortuous coronary vascular segments. Immediate success rates in this setting, resulting in a widely patent lumen, have been greater than 90%. DCA has also found application in occluded saphenous vein grafts after coronary artery bypass surgery with excellent early success[37]. One of the great advantages of DCA has been retrieval of specimens for analysis and study of the pathology of atherosclerosis and restenosis. Cells from atheromatous plaques have been isolated from atherectomy specimens and have been successfully cultured, providing insight into the cellular nature of atherosclerosis and restenosis. These differences in cellular phenotype have found much clinical application. Recently, *in situ* hybridization studies of atherectomy specimens have identified a marker of increased risk of restenosis in certain subgroups of atherosclerotic plaques[38].

One of the major limitations to atherectomy, as with most interventional techniques, is restenosis, with rates ranging from 35% to 50%. Theories have been postulated regarding the issue of restenosis. It is believed that simple balloon dilatation could be a contributing factor to vessel wall injury that elicits a restenotic proliferative response. Another factor that may have a role is the depth of tissue resection. It was shown that resections limited to the intima resulted in the lowest restenosis rates at 34% while full-thickness resection through to adventitia yielded an increased rate at 54%[37]. It has been reported that vessel wall perforations may occur, but are rare.

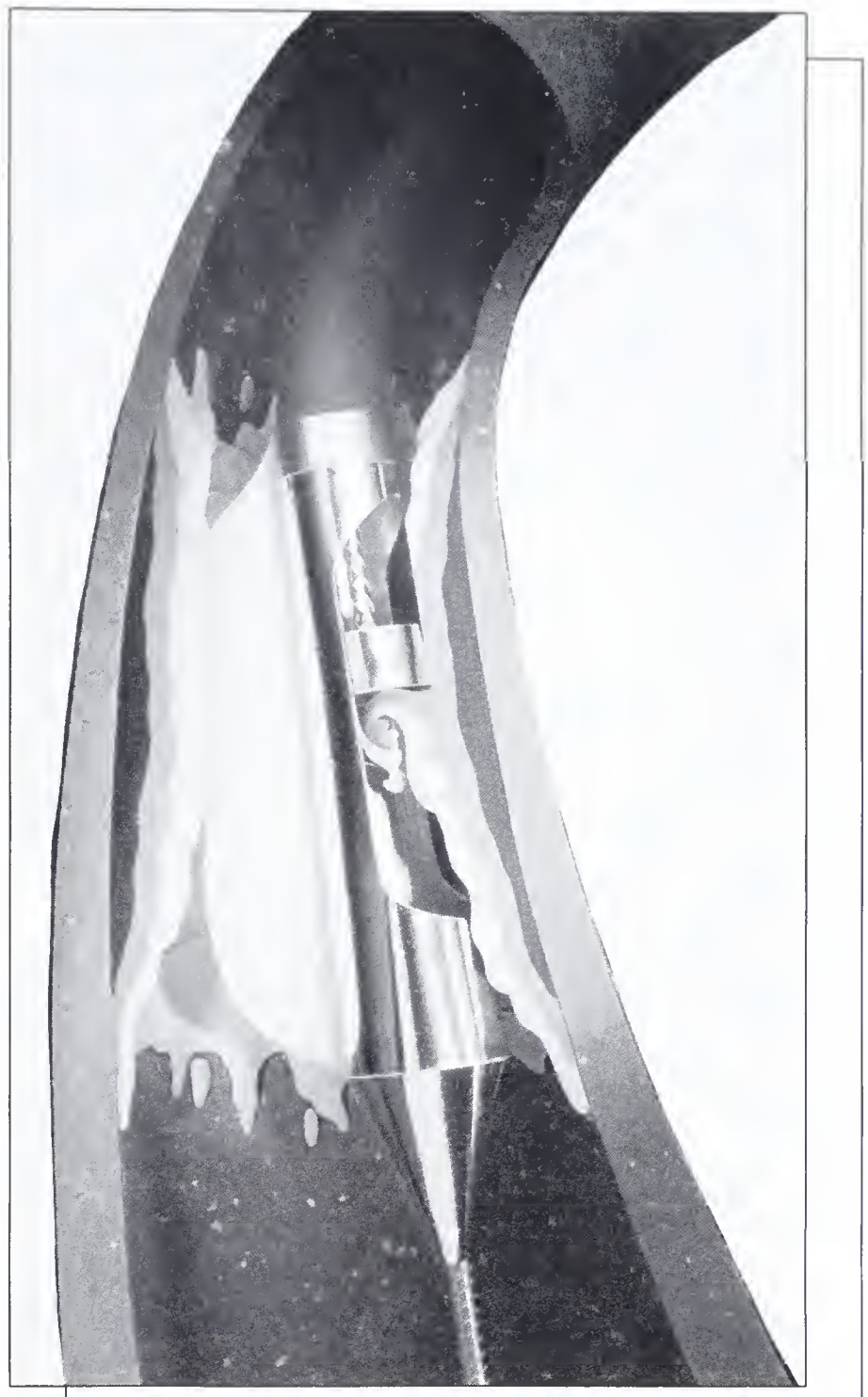
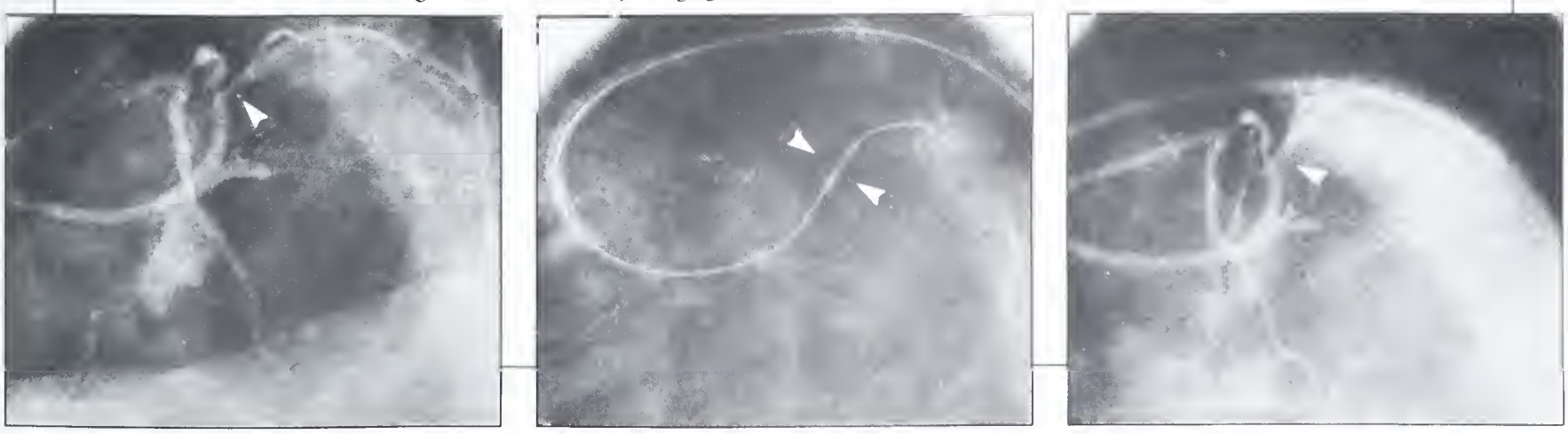


Figure 4a: Removal of plaque with atherectomy catheter.

Atherectomy has been compared to PTCA, the standard at the present time. Success rates and complication rates are comparable to conventional balloon angioplasty, but there are differences based on device design. The size and rigidity of the atherectomy catheter precludes its use in unfavourable lesions which may well be amenable to PTCA. DCA may cause more ischemia and pain during the procedure than PTCA since it produces an impediment to coronary blood flow even with the balloon deflated[39]. Comparisons of matched lesions have demonstrated that DCA produces

Figure 4b: Atherectomy. Angiograms taken before, during, and after atherectomy.



a larger initial absolute lumen diameter than PTCA with less residual stenosis and a greater calculated flow reserve across the stenosis[39-41]. A decreased incidence of coronary dissection has also been reported with less lumen compromise by intimal flaps[42]. Thus, DCA is associated with an improved immediate angiographic result compared with angioplasty. Two large trials of atherectomy versus angioplasty were undertaken in the United States (Coronary Angioplasty Versus Excisional Atherectomy Trial or CAVEAT)[43] and Canada (Canadian Coronary Atherectomy Trial or CCAT)[44]. These studies confirmed that initial angiographic results were superior with atherectomy but there was a larger late loss resulting in similar minimal lumen diameter at follow-up and comparable rates of restenosis.

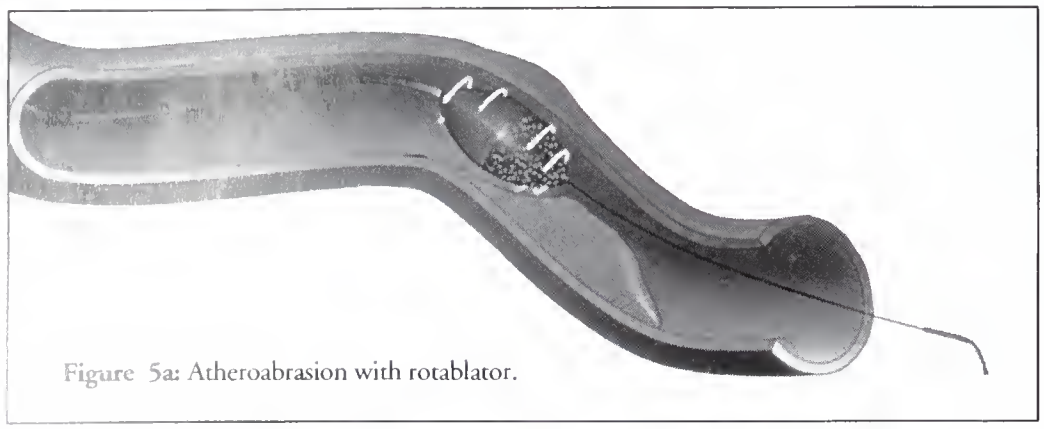


Figure 5a: Atheroabrasion with rotablator.

Another tissue removal device is the rotablator, which operates by an atheroabrasion mechanism (Figures 5a and 5b). Rapid rotation of an abrasive burr coated with 30 to 40 μm diamond chips rotating at a rate of 150,000 to 175,000 rpm is effected by a turbine driven by compressed air[37]. The tip pulverizes the atheroma into particles usually smaller than 5 μm which are then showered distally, enter the coronary microcirculation, and are removed from the circulation by the reticuloendothelial system[36]. An immediate problem is the fact that 5-10% of microfragments are large enough to cause occlusion of small vessels downstream with subsequent microinfarction[45] or the so-called "no-reflow phenomenon".

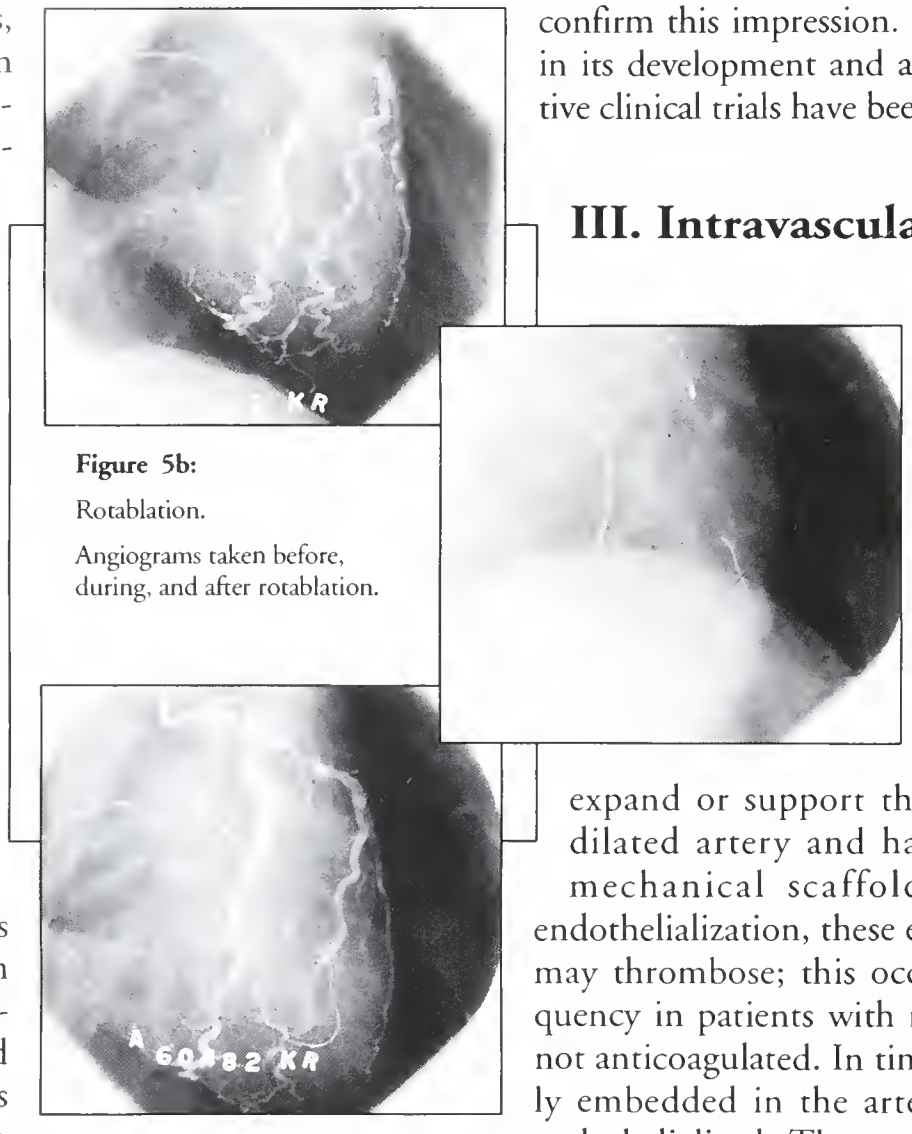


Figure 5b:
Rotablation.
Angiograms taken before, during, and after rotablation.

Acute complications of rotablation include non-Q wave myocardial infarction, thrombotic occlusions and transient episodes of ischemia, AV block, and coronary vasospasm[46]. The incidence of dissection is lower with rotablation (8%) than PTCA (30-40%), but rates of restenosis in non-randomized studies are equivalent or higher[48,49].

Rotablation may be preferable for complex lesions[50] and heavily calcified coronary artery disease[51] because of its ability to create a smooth lumen without deep cuts into the wall of the vessel[45,51,52]. Ostial lesions may also be amenable to rotablation because of the light elastic content of these lesions, but randomized trials will be necessary to confirm this impression. Rotablation is still early in its development and as yet, no large prospective clinical trials have been completed.

III. Intravascular Stents

The term "stent" actually derives from the name of a 19th century English dentist, C. Stent. It is a device that is used to maintain the opening of an orifice or cavity in the body of the patient. In interventional cardiology, stents are used to expand or support the internal lumen of a dilated artery and have been likened to a mechanical scaffold. Early on, before endothelialization, these endovascular prostheses may thrombose; this occurs with 10-25% frequency in patients with metallic stents who are not anticoagulated. In time, stents become firmly embedded in the arterial wall and become endothelialized. These stents are stainless steel alloys that are made into a woven wire or continuous mesh which are then delivered to the appropriate site and expanded to the proper diameter (either balloon-expanded or self-expanded) (Figures 6 and 7).

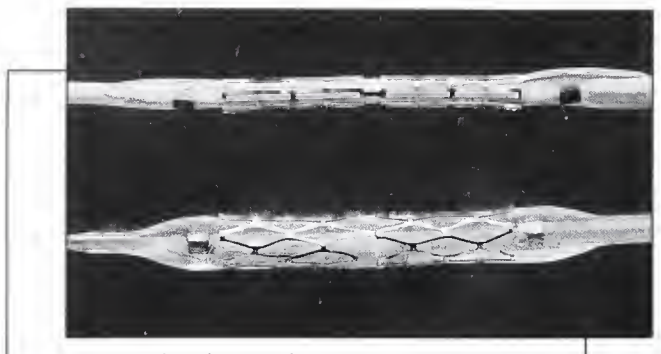


Figure 6: Palmaz-Schatz coronary stent before and after balloon inflation.

The role of stents has been limited to two major uses as adjuncts to PTCA[53]. One is to reopen an occluded artery immediately after failed angioplasty. The other has been to attempt to mitigate restenosis or recurrent occlusions after balloon angioplasty. Thus, dissections post-PTCA may be managed with stents, but vessel wall injury caused by the stent itself may have a proliferative restenotic response[54]. A

Figure 7: Intracoronary stent. Angiograms taken before, during, and after stent placement.

North American restenosis trial (Stent Restenosis Trial or STRESS) randomized 407 patients to balloon angioplasty or primary stenting (Palmaz-Schatz stent) and the results have been presented in a preliminary fashion[55]. It showed a significantly lower restenosis incidence in the stent group (29%) compared to the PTCA patients (43%) ($p<0.01$). This was the first study to show (using quantitative angiography) that all the gain by a new device was not lost in follow-up. Post-stent, the minimum lumen diameter at the treated site was 2.47 ± 0.44 mm compared to 1.92 ± 0.51 mm after PTCA. At follow-up, there was a greater loss of 0.70 mm in the stent patients versus 0.39 mm in the PTCA patients but the final diameter in the stent patients was still better at 1.77 ± 0.59 mm versus 1.53 ± 0.64 mm.

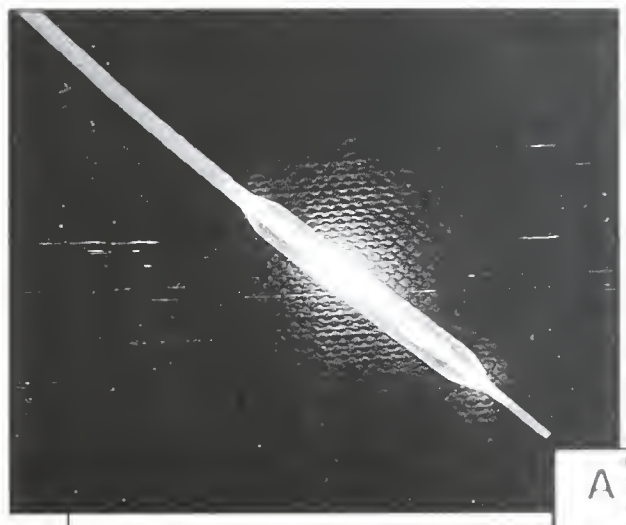


Figure 8: Laser angioplasty catheter.

The major drawback of stents has been thrombosis[56]. This may be secondary to suboptimal anticoagulation, thus vigorous anticoagulation is now recommended. At implantation, aspirin, dipyridamole, dextran, and heparin are used with post-procedural maintenance of antiplatelet agents for three months and warfarin for one month[53]. Heparin-bonded and bioabsorbable stents have also been described to reduce thrombotic complications[57]. Bioabsorbable compounds such as polylacturonate or polyethylene terephthalate and other polymeric stents may also allow for drug delivery systems in a locallized part of the vasculature[58].

IV. Laser Angioplasty

Lasers have been used in medicine for many years. Lasers applied to the treatment of coronary artery disease may vapourize atherosclerotic plaque with minimal disruption of the plaque and minimal stretch of the vessel wall. This would allow re-vascularization of lesions that are unfavourable for conventional balloon angioplasty[37] (Figures 8 and 9). In terms of safety and efficacy, the only justification for using lasers invasively would be in overcoming the limitations of balloon angioplasty (restenosis, chronic occlusions, and diffuse disease).

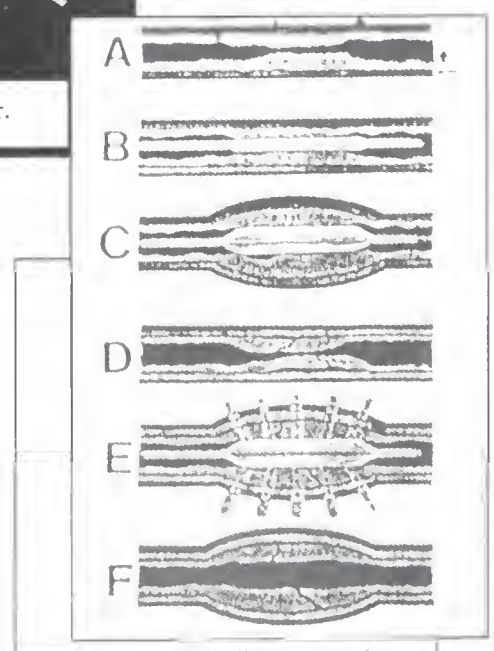


Figure 9: Laser balloon angioplasty.

Atheromatous tissue preferentially absorbs in the 450 nm to 480 nm wavelengths, thus certain pulsed excited dye lasers may enable atheroma ablation with minimal damage to normal tissues[59]. The selectivity for atheroma may be further improved by the use of adjuvants that are actively taken up by atheromatous tissue, including tetracycline[60] and hematoporphyrin[61].

The mechanisms of tissue ablation are three-fold: photothermal effect, photoacoustic trauma and photochemical effect[37]. The predominant mechanism of tissue destruction is photothermal. The laser is absorbed by the tissue and is converted into heat which raises intracellular temperature leading to denaturation of proteins, nucleic acids and membranes and vapourization of intracellular water. Photoacoustic damage is secondary to explosive rupturing of cell membranes as a result of rapid production of water vapour. This has a shock wave effect which injures surrounding cells, resulting grossly in a central crater surrounded by a rim of carbonization. The valleys of the crater are eventually filled with ingrowing endothelial and smooth muscle cells. The photochemical effect is related to the breakage and disruption of chemical bonds, which is described by some to be the primary mechanism of action of excimer pulsed lasers.

One of the initial applications of lasers in interventional cardiology was in laser balloon angioplasty. The system employs a Nd-YAG laser inside a modified balloon catheter which allows circumferential delivery of laser thermal energy. The balloon is inflated to perform angioplasty, then pulses of laser radiation are delivered into the balloon and transmitted through the balloon material to the vessel wall, raising tissue temperature in the range of 80°C to 120°C. The tissue is allowed to cool while the balloon remains inflated and the vessel sets. Elastic recoil is reduced[62]. There is thermal fusion of intimal tears and dissections[63] and given the laser's dessicating effect on thrombus, there may be decreased thrombogenicity[64]. Clinical trials have reported success with laser balloon angioplasty in reopening acute occlusions after PTCA due to dissection or thrombus, thus avoiding the need for emergency bypass surgery[65]. Laser balloon angioplasty is effective in increasing minimal lumen diameter beyond that of balloon angioplasty alone and has been shown to have satisfactory early clinical results[66,67].

The problems with a thermal system are many and have included perforation, spasm, thrombosis, embolism and branch vessel occlusion[68-70]. These may be addressed with antispasm and anticoagulation measures[71]. Other reported complications include transient bradycardia, hypotension (reversible with atropine) and ventricular fibrillation[66]. Restenosis is still problematic, with relatively high rates during short-term follow-up[66,72].

Pulsed excimer lasers are an improvement upon the older thermal systems. Pulsed excimer lasers have minimal thermal effect and thus only little damage to surrounding tissue occurs. This has resulted in fewer thermal complications including reduced coronary vasospasm and thrombosis. One additional benefit is the ability of the excimer laser to ablate calcified plaque[73], a deficiency of continuous wave thermal systems[68,74]. Considering the above benefits, excimer laser systems may show promise in the future and are currently the most commonly used lasers for coronary recanalization.

Conclusions

One cannot ignore the array of new interventional modalities available or currently under investigation. Success rates with these new devices are high, ranging from 80% to 90%. Some of this success is related to the experience of investigators who have become expert in the conventional methods of PTCA and the advanced diagnostic support available. There are complications, some of which are common to many modalities and some which are unique to particular methods. The problems in common are branch vessel occlusion, necessity of urgent coronary bypass graft surgery and myocardial infarction. Perforation with atherectomies and stent dislodgement are more specific to the method employed, but are still quite important problems to be addressed. The major complication that is seen with all approaches is restenosis. Most new approaches are subjected to head-to-head randomized studies against conventional angioplasty and the results of these studies will define the ultimate role for these modalities.

Clinical indications for PTCA have been defined to be significant stenosis of one or more epicardial arteries subtending at least a moderate-sized area of viable myocardium in a patient who has : (1) recurrent ischemic episodes after myocardial infarction or major ventricular arrhythmia, (2) angina that has not responded adequately to medical therapy, (3) clear evidence of myocardial ischemia on resting, ambulatory, or exercise ECG, or (4) objective evidence of myocardial ischemia that increases the overall risk of required non-cardiac surgery[1]. Indications for the other techniques are not as well-defined, but may become clearer with further clinical efforts in this field.

From a practical perspective, one must be cognizant of the fact that PTCA is a relatively effective and efficient invasive procedure in a varying range of ischemic coronary artery diseases. Despite this, PTCA has four major deficiencies: decreased efficacy in chronic occlusions, acute closure complications, lack of efficacy in diffuse disease, and restenosis. Chronic occlusions present problems because of difficulty in wire crossing which is the necessary first step of any intervention and diffuse disease is difficult to treat because of the focal nature of PTCA. Acute closure occurs in only 5-7% of cases but is associated with increased morbidity and mortality, necessitating urgent coronary bypass graft surgery. Restenosis appears to be a general response to the injury effected by the intervention itself and although it still remains unaltered, it is likely that it will at least be partially solved by a combination of new devices, pharmacology, and molecular biology. New interventional methods may be of little additional benefit unless they can be shown to be unequivocally superior to PTCA in one of these four areas of concern.

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Chronic Pain Following Ankle Sprains: Aetiology, Classification, and Management

Michael K. Gilbart (9T5) and Darrell J. Ogilvie-Harris, M.D., F.R.C.S.(C).*

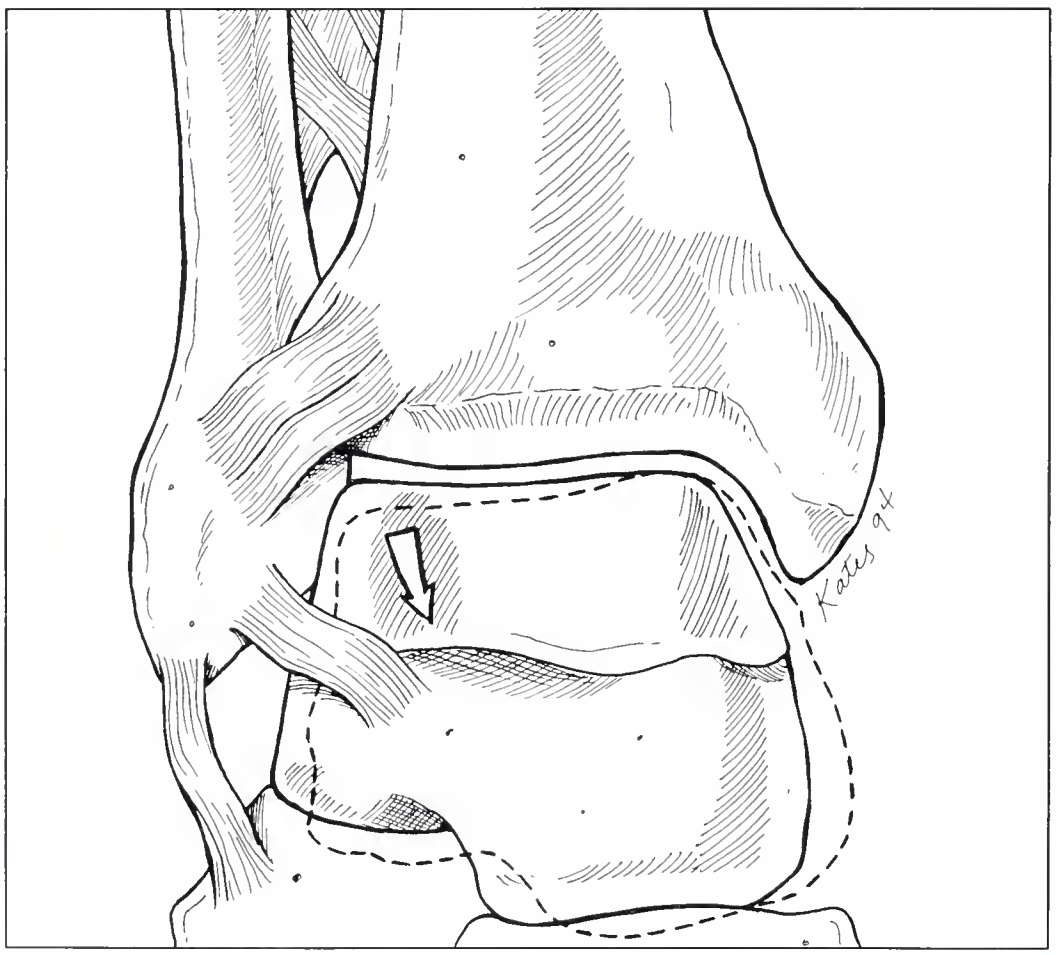
*Associate Professor, Department of Surgery; Chief, Orthopaedic Surgery, The Toronto Hospital, Western Division

Abstract

Persistent pain in the ankle joint may be encountered after acute injuries or excessive use of the joint (e.g. sports-related trauma). If symptoms persist beyond the normal time frame for healing (6 months), the use of ankle arthroscopy may become necessary for diagnosis and treatment. Arthroscopy was performed after appropriate investigations on 100 patients with a history of chronic ankle pain for more than 6 months following an inversion injury. A new classification system of the etiologies of chronic ankle pain was generated, based upon six pathological types. The pathology in 93 of the 100 ankles studied could be categorized into one of three groups: instabilities (lateral and syndesmotic); impingements (anterior and anterolateral); or osteochondral lesions and loose bodies. Seven patients had non-specific osteoarthritis and/or synovitis on arthroscopy. The best results of arthroscopy were obtained for the treatment of loose bodies (100%) and anterior impingement (90%). This paper discusses the classification system, as well as the important diagnostic steps (including physical exam and investigations) involved in differentiating among these different causes of chronic ankle joint pain. The indications for operative arthroscopic intervention are outlined, as well as the potential complications reported in the literature. Ankle arthroscopy appears to be a very useful diagnostic and therapeutic tool in carefully selected patients who have not responded to conservative therapy.

Introduction

Ankle injuries are among the most common injuries seen in sports medicine. These injuries are not always trivial, and may result in considerable morbidity and financial cost[1]. It has been estimated that 25-40% may be associated with recurrent functional instability or prolonged disability[2,3].



WENDY KATES

Conservative management is recommended for most foot and ankle injuries and inversion sprains of the ankle should be treated conservatively for at least 6 months before operative intervention is considered[1,4]. General management principles of acute soft tissue injury begin with rest, ice, compression, and elevation (RICE)[2]. Once the inflammation, edema, and pain have begun to subside from the acute injury phase, active assisted movement and passive stretching exercises should be initiated. Non-steroidal anti-inflammatory medication may also be useful for a number of patients[5]. Further therapy includes active range of movement exercises, strengthening, and proprioceptive training (e.g. with a balance board and multidirectional wobble board) to regain normal function of the ankle[6]. Considerable improvement should be noticed by 6 weeks post-injury[1,4]. If symptoms persist beyond a 6 month period, the likelihood of success with further conservative management diminishes, and ankle arthroscopy should become a consideration for further treatment.

Classification and Clinical Spectrum

While chronic ankle pain is a fairly common clinical presentation, a classification of the causes of such ankle pain has not been described previously. The joint pathology typical of patients experiencing chronic ankle pain refractory to conservative treatment may be categorized into one of three groups of pathophysiological types: instabilities, impingements, or chondral injuries. These will be discussed along with the findings on physical exam and investigations characteristic for each type of pathology (see Table 1).

Table 1

Diagnostic Criteria for Ankle Joint Pain

Syndrome	Physical Exam	Investigations
Lateral Instability	1. increased talar tilt on inversion stress 2. positive anterior drawer sign	lateral stress X-ray (increased talar tilt >5 degrees)
Syndesmotic Instability	1. tender over syndesmosis 2. positive squeeze test 3. positive syndesmotic stress test 4. positive external rotation stress test	positive bone scan (in syndesmosis)
Anterior Impingement	1. pain and limited dorsiflexion	lateral X-ray (ant. bone spurs)
Anterolateral Impingement	1. pain on plantarflexion over anterolateral joint	MRI (synovial thickening)
(Osteo)chondral Fractures	* no specific tests	X-ray (osteochondral fragments)
Loose bodies	1. sense of "locking"	X-ray (loose calcified fragments)

1. Instabilities

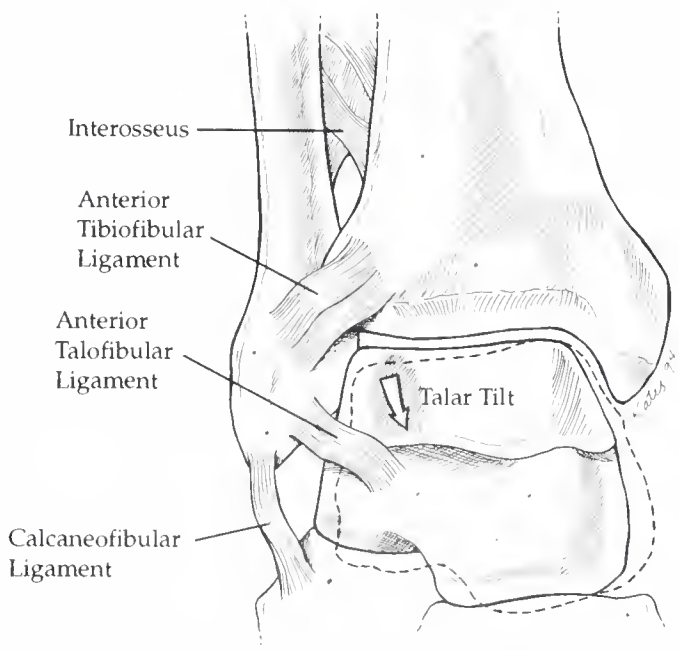
There are three main groups of supporting ligaments stabilizing the ankle that can be subjected to trauma and sprains: the lateral ligaments, the syndesmotic ligaments, and the medial deltoid ligaments. Injury to the lateral or syndesmotic ligaments may result in chronic dysfunction of the ankle joint. The most common presenting history of instability includes chronic ankle pain with ambulation, weakness, and frequently a sensation of giving way.

(a) Lateral

The ankle joint is stabilized laterally by the anterior and posterior talofibular and the calcaneofibular ligaments. Typically, supination injuries with the ankle in plantarflexion cause damage to the primary stabilizer of the ankle, the anterior talofibular ligament. With greater force of injury or adduction movements the calcaneofibular and posterior talofibular ligaments may become damaged. When most or all of these ligaments are damaged, the ankle joint becomes unstable. These ligaments usually heal, but may have pathological residual laxity associated with them, causing increased talar tilt (Figure 1) and signs of mechanical instability.

On physical examination, these patients have the sensation of an "unstable" ankle and typically feel pain upon forced supination of the ankle (with or without plantarflexion). They have laxity on inversion stress with increased talar tilt (Figure 2a). Usually there is an anterior drawer sign (Figure 2b). The diagnosis of lateral instability may be confirmed with a lateral stress roentgenogram (mortise view) of the ankle, which shows an increase in lateral talar tilt of the ankle mortise by 6 or more degrees[7]. Arthroscopy is helpful in this diagnosis and can be used to demonstrate the abnormal talar tilt. Chondral fractures are often seen with chronic lateral laxity and can be excised arthroscopically. However, definitive treatment of the lateral instability requires open surgical repair of the lateral ligaments, for which several procedures (e.g. Elmslie, Evans, Christman and Snook) have been described[8,9,10,11].

Figure 1: Pathology causing ankle joint pain: instabilities.



(b) Syndesmotic

The syndesmotic ligaments function to hold the tibia and fibula together and to maintain mortise stability, especially during dorsiflexion with weight bearing[12]. They are composed of the anterior and posterior tibiofibular ligaments (the primary stabilizers) and the transverse tibiofibular and interosseous ligaments. As with lateral instability, healing of these syndesmotic ligaments with residual excess laxity may cause mechanical instability of the ankle mortise and pain (Figure 1).

On physical examination, these patients are often tender on palpation over the anterolateral portion of the distal tibia. They also experience pain upon squeezing the proximal tibia and fibula together firmly, thereby stressing the syndesmosis (positive squeeze test). Pain can be elicited by exerting anterior-posterior stress on the syndesmosis with movement of the medial and lateral malleoli in

Figure 2: Physical exam tests for chronic ankle pain

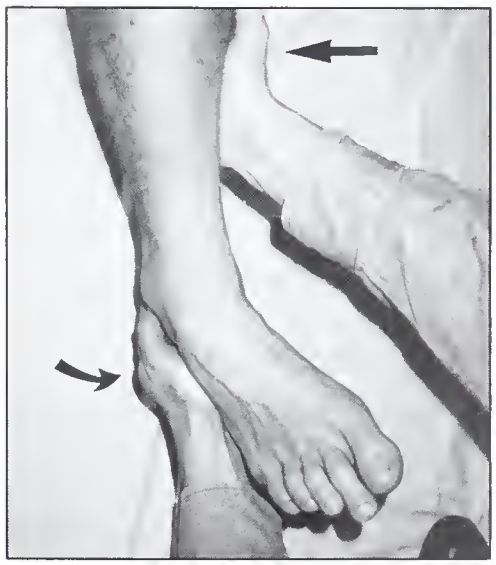


Figure 2a: Inversion stress test. Examiner places one hand on the calf and with the opposite hand grasps the talus and calcaneus, applying an inversion strain. An increased talar tilt occurs with lateral instability.

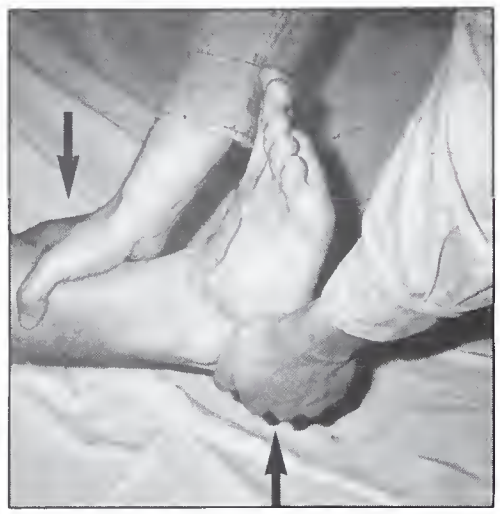


Figure 2b: Anterior drawer test. Examiner places one hand anteriorly on the distal tibia and cups the calcaneus with the opposite hand. The calcaneus and talus are forced anteriorly. Anterior subluxation of the talus on the tibia occurs with lateral instability.

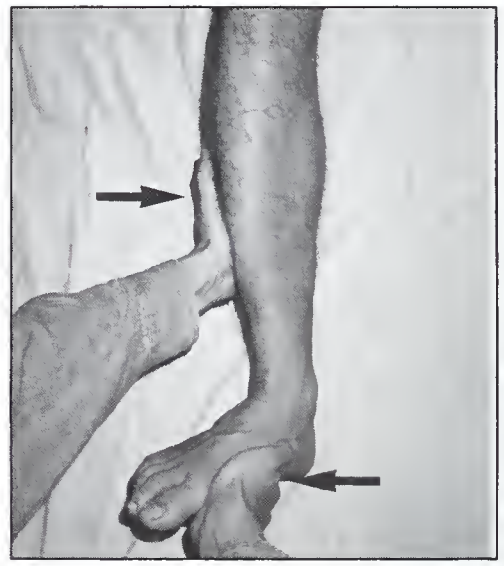


Figure 2c: External rotation stress test. Examiner places the ankle in neutral dorsiflexion. One hand is placed at the mid-calf level, while the opposite hand grasps the medial portion of the midfoot and externally rotates the ankle. Pain is elicited over the syndesmosis with syndesmotic instability.

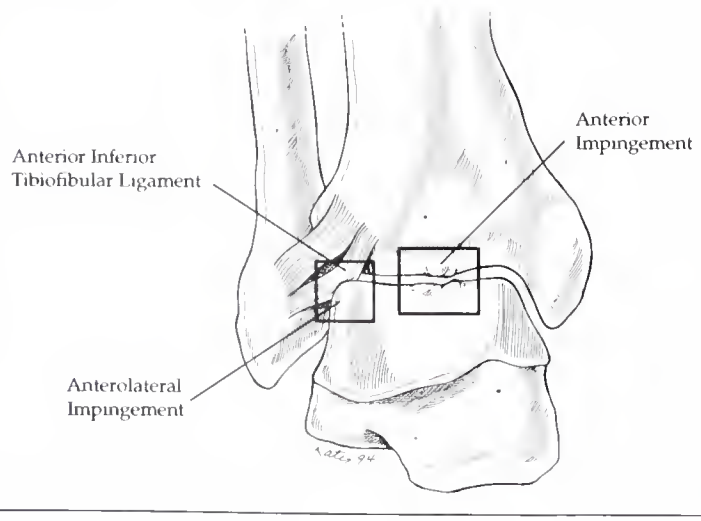
opposite directions (syndesmotic stress test). A third test is the external rotation stress test in which the ankle is held in neutral dorsiflexion and externally rotated to put force on the fibula (Figure 2c). This stresses the syndesmosis and pain indicates a positive test. Diagnostically, a positive bone scan in the area of the syndesmosis, as well as these symptoms of pain, is indicative of syndesmotic instability. The presentation of syndesmotic instability is thus quite different than that of lateral instability. Arthroscopic treatment involves the resection of any torn or loose portions of the syndesmotic ligaments.

2. Impingements

(a) Anterior

The anterior impingement syndrome was first described by Morris and McMurray in the 1940's as "athlete's" or "footballer's" ankle[13,14]. It generally describes a bone spur (cartilage-capped bony projection) formed on the anterior lip of the tibia and a corresponding spur on the dorsum of the talar neck (Figure 3). The cause of anterior spurring is unknown, yet this may develop as a result of recurrent microtraumas to the joint capsule with maximum plantarflexion of the foot[15]. It has also been suggested that repeated forced dorsiflexion, as occurs during running, dancing, and other sports, may lead to these exostoses at points of contact between the tibia and talus[16].

Figure 3: Pathology causing ankle joint pain: impingements.



On physical examination, dorsiflexion of the ankle forces the talar and tibial exostoses together, blocking further movement and causing pain. These exostoses may be visualized on lateral roentgenograms of the ankle. Arthroscopic resection using a burr is usually very successful in treating osteophytes of the ankle and reshaping the involved tibial or talar surfaces[17].

(b) Anterolateral

The anterolateral impingement syndrome develops as a result of impingement of an enlarged distal fascicle of the anteroinferior tibiofibular ligament on the anterolateral aspect of the talus (Figure 3). The ligament is enlarged due to fibrosis as a result of reactive inflammation associated with an acute sprain. A chronic reactive synovitis and chondromalacia of the lateral talar dome often develop as a result of the impingement as well[18].

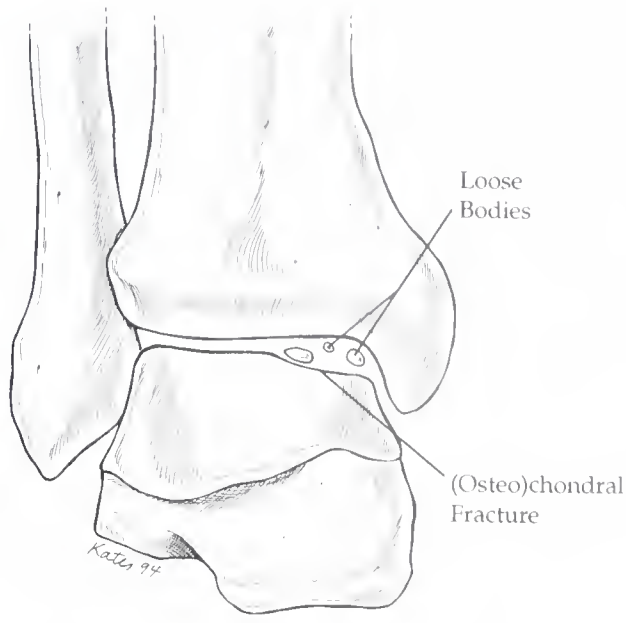
On physical examination, pain can be elicited on passive forced ankle plantarflexion. MRI is the most useful diagnostic screening test, showing synovial thickening consistent with impingement in the anterolateral gutter. Arthroscopic treatment involves resection of the hypertrophied fascicle of the anteroinferior tibiofibular ligament and partial synovectomy.

3. Chondral injuries

(a) Chondral and osteochondral fractures

Chondral and osteochondral fractures are usually the result of trauma to the ankle joint and generally cause symptoms acutely (Figure 4). Where there are chronic symptoms, especially involving the posteromedial talus, osteochondritis dissecans may be present[15]. The cause of osteochondritis dissecans is considered to be avascular necrosis of a portion of subchondral bone, with eventual separation of a loose fragment of cartilage and subchondral bone[19].

Figure 4: Pathology causing ankle joint pain: chondral injuries.



There are no specific tests or signs on physical exam which are characteristic of this condition. X-rays of the ankle may be useful to visualize this pathology, but if articular cartilage is involved exclusively, it may not be apparent. The arthroscopic treatment of these consists of the removal of the osteochondral fragments and curettage and debridement of the pathological portions of the articular surface.

(b) Loose bodies

If there has been a recent trauma, chondral or osteochondral fragments can break off and spread through the joint (Figure 4). By subsequently increasing in size, these can later lead to locking and pain. Diagnosis may be aided by roentgenograms if the loose bodies are calcified. Treatment involves arthroscopic removal of the loose bodies.

Osteoarthritis and synovitis

The presence of osteoarthritis and synovitis in the ankle joint is not necessarily a result of ankle joint trauma caused by sprains. Osteoarthritis is characterized by degenerative changes of the articular cartilage surface (fibrillation). These may develop as a chronic result of an acute osteochondral lesion, such as a fracture, or as a result of repeated, minor trauma to the articular surfaces[20]. Synovitis may develop as a result of a reactive process intra-articularly in response to osteophytes or loose bodies[21]. Chronic synovitis may lead to degenerative changes in the articular cartilage surface and thus should be treated.

Arthroscopy

Ankle arthroscopy provides diagnostic information not available by conventional clinical and radiographic investigations. In a recent study, ankle arthroscopy was shown to be quite adequate in identifying intra-articular pathology, with 94% of arthroscopic diagnoses being confirmed by arthrotomy[22]. In general, this technique provides visualization of the entire joint space, while offering fewer complications, less post-operative morbidity, and an overall faster rehabilitation and return to normal function[23]. A number of orthopaedic procedures once performed as open arthrotomies may now also be performed with the aid of the arthroscope. These include arthroscopic removal of loose talar dome or tibial plafond fracture fragments (with curetting or drilling of the base), arthroscopic removal of loose bodies, lysis of adhesions, and synovectomy[21,24]. Ankle arthroscopy constitutes approximately 2% of all arthroscopic procedures[25].

Complications

Complication rates for ankle arthroscopy vary drastically in the literature, from 17% to only a few percent[15]. Possible complications include temporary paresthesias or permanent sensory losses, chondral lesions due to the incorrect handling of instruments, compartment syndrome, post-operative hemarthrosis, and superficial or deep infection[20]. In fact, there appears to be a greater risk of complications in arthroscopy of the ankle joint than in arthroscopy of other joints[21].

Indications for Arthroscopic Surgery

The indications for ankle arthroscopy in patients includes a prolonged history of ankle pain refractive to conservative therapy, plus any or all of the following: intermittent locking, instability, swelling, stiffness, limping, a decrease in normal activities, or the presence of radiographic abnormalities[21].

Table 2

Scoring System Used to Assess Results in Five Categories

	1 Poor	2 Fair	3 Good	4 Excellent
Pain	Severe	Moderate	Mild	None
Swelling	Moderate/severe	Mild with ADL *	With exercise	None/Minimal
Stiffness	Minimal motion	Painful deficit	Mild deficit	None-minimal
Limping	Severe (cane/crutch)	Moderate	Slight	None
Activity	Limited ADL	Moderate limits	[illegible]	No limits

*activities of daily living

Arthroscopic Treatment Results

One hundred consecutive patients were followed prospectively as the basis of this study. Patients were selected for arthroscopy by the senior clinician based on the indications for surgery noted above. They all underwent arthroscopy of the ankle on an outpatient basis. An ankle scoring system based upon five categories (pain, swelling, stiffness, limping, and activity) was used to assess patients at follow-up assessment (Table 2). Patients were classified as having a successful result if they were able to return to all or most of their pre-injury activities and had no pain or occasional pain (i.e. "good" to "excellent" - groups 3 and 4 of scoring system).

Table 3

Arthroscopy Results

Diagnosis	Number	Success	%
Syndesmotic instability	9	6	67
Anterior impingement	11	10	90
Anterolateral impingement	17	13	76
Chondral fractures			
with instability	9	3	33
without instability	12	10	83
Loose bodies	5	5	100
Non-specific synovitis/OA	7	3	43
Total	**70**	**50**	**71**

Arthroscopic surgery on the ankle was performed in all 100 patients for diagnostic purposes. Treatment was also performed arthroscopically in 70 of these patients. The remaining 30 patients had chronic lateral ligamentous instability and were instead treated definitively with an open surgical repair of the ligaments (i.e. Evans repair)[7]. Of the 70 patients treated arthroscopically (Table 3), 71% were successfully treated, based upon their ability to return to all or most sports and the presence of little or no ankle pain after such sports. The minimum follow-up time for these patients was 2 years. The best results were obtained in the treatment of loose bodies (100%) and anterior impingement (90%). The success rates of treatment of chondral fractures with instability and non-specific synovitis/osteoarthritis were 33% and 43%, respectively. These were not as successful as other treatments, likely due to their chronic, degenerative nature.

There were 3 complications in the 100 patients treated with ankle arthroscopy. Two patients had mild numbness around the medial arthroscopic portal and eventually recovered. One patient developed a local infection at the medial arthroscopic portal which went on to heal after antibiotic treatment.

Conclusions

Arthroscopy allowed excellent inspection of the entire ankle joint and visualization of the pathology present. Arthroscopic findings also enabled the classification of the pathological causes of chronic ankle joint pain after injury to the ankle. These may be divided into one of three groups of two: the instabilities (lateral and syndesmotic), the impingements (anterior and anterolateral), or the osteochondral fractures and loose bodies. In all cases of chronic ankle pain conservative treatment should be attempted for at least 6 months, after which time arthroscopic treatment may be considered as a necessary alternative. Our results also indicate that ankle arthroscopic treatment gives good relief of some causes of chronic ankle pain after an inversion sprain of the ankle.

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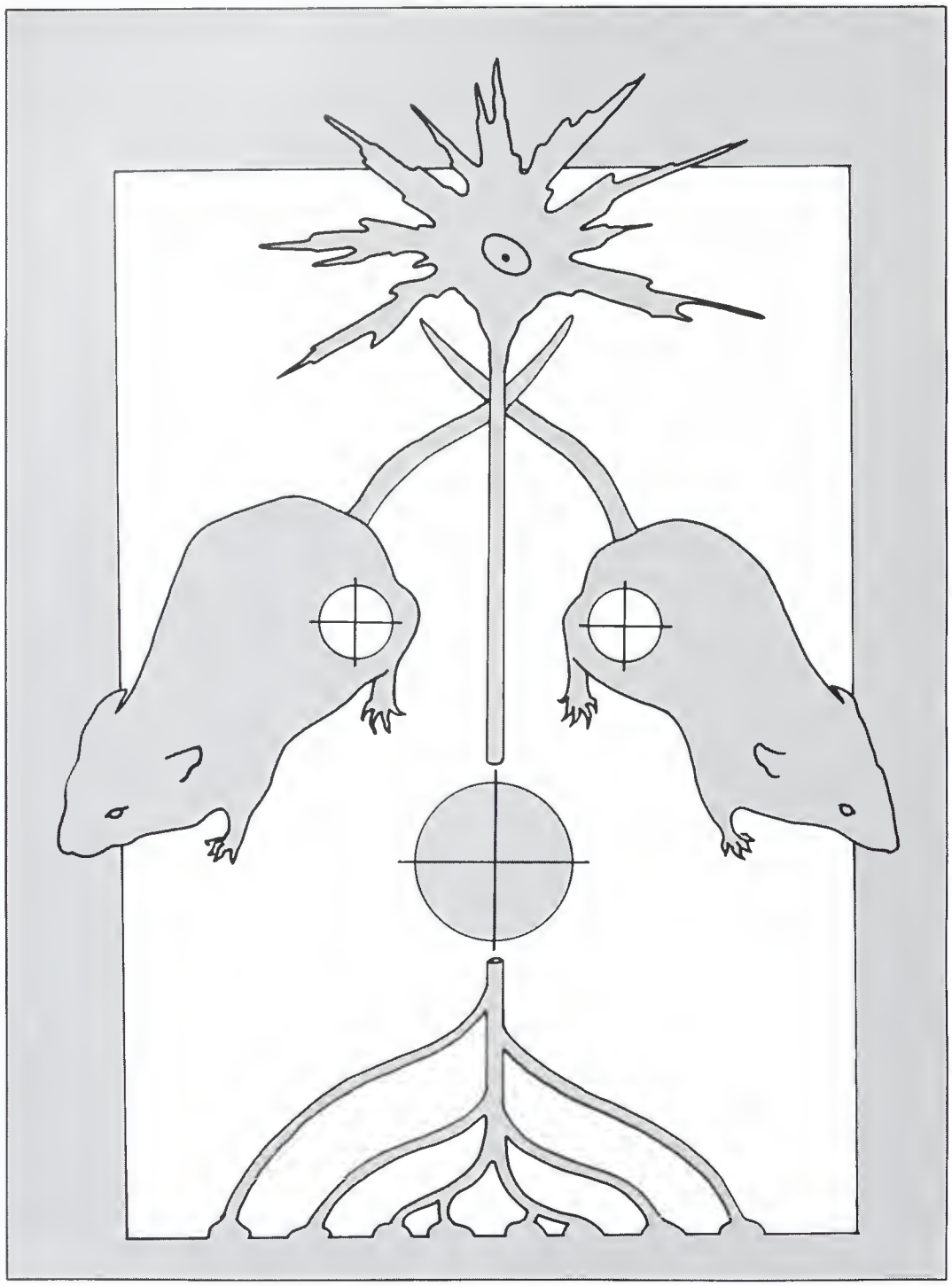
Neuronal Gene Expression in Aged Rats During Regeneration

James N. Scott, M.Sc. (9T4) and Irma M. Parhad, M.D.*

* Associate Professor, Departments of Pathology & Clinical Neurosciences, University of Calgary, Calgary, Alberta

Abstract

Various studies have shown that axonal regeneration and sprouting are retarded with aging. Axonal elongation and sprouting have been directly correlated with expression of known cytoskeletal and growth-associated proteins (GAPs), including α_1-tubulin and GAP-43, respectively. This study evaluates whether this retardation with aging is related to a decline in expression of these growth-associated proteins. Northern analysis was performed on L4-L5 dorsal root ganglia (DRG) of young (3 month) and aged (23 month) rats following a sciatic nerve crush and compared to their age-matched controls. The results show that initial mRNA levels of α_1-tubulin and neurofilament light subunit (NF-L) in the control aged rat DRG were half those of the control young adult, whereas expression of GAP-43 was equivalent. Two weeks after axotomy, the expression of α_1-tubulin and GAP-43 in the aged DRG was found to be induced to the same levels as in the axotomized young adult, and the expression of NF-L was decreased proportionately in both age groups. These results suggest that, although differences may exist in the constitutive expression of these genes with advancing age, the aged neuron is as capable as the young adult neuron in regulating its gene expression following axotomy. Therefore, this ability of aged neurons further suggests that factors other than the control of gene expression must be responsible for their diminished rate of axonal regeneration.



JUDY SHERWOOD

Introduction

Axotomy of peripheral mammalian axons induces a variety of metabolic changes in the neuronal cell body which support the process of axonal regeneration[1]. During this process daughter axons sprout, elongate distally, restore functional connections of their peripheral axons, and finally mature via radial growth. The neuronal cytoskeleton plays an essential role throughout regeneration by providing the basis of motility, structure, and stabilization of the newly formed axons. In order to accommodate the intense demands placed upon a regenerating

neuron, major changes in the biosynthesis and export of cytoskeletal and membranal components such as microtubules, growth-associated proteins (GAPs), and neurofilaments (NFs) must occur.

Regeneration in young animals is associated with a characteristic profile of gene expression that, in general, is similar to the profile seen during development. In both of these instances, there is enhanced synthesis of substances that are abundant in elongating axons, such as tubulin and GAPs[2-6]. In contrast, substances which are less important for axonal elongation, such as the NF proteins which regulate axonal calibre[7], have their synthesis down-regulated until the target tissue is reached[3-8]. At the time of re-innervation, the NF mRNA and protein levels recover and contribute to the maturation and increase in axon diameter[3,4,7].

The age of the animal influences both the ability of the neuron to survive after axotomy and the rate of regenerative outgrowth. Axotomy during embryonic and early postnatal development generally results in neuronal death, whereas axotomy after that period is more often associated with neuronal survival and effective axon regeneration[1,9]. However, following axotomy in aged animals, the process of peripheral regeneration and recovery of function is delayed, although it is eventually as complete as in younger animals[10-12]. The reason for this delay is uncertain but may be related to factors extrinsic to the neuron, including the interactions with supporting[12-14] and target cells[15], or the presence of required growth-stimulating signals[16]. Alternatively, this may be related to factors intrinsic to the neuron, such as alterations in normal cellular function[9,10] or in the control of gene transcription[17].

The present study examines the effects of advancing age on neuronal mRNA expression in dorsal root ganglion (DRG) neurons during peripheral nerve regeneration; to ascertain how advancing age affects the neuron; and to determine whether the aged neuron, in response to a substantial metabolic challenge such as the regrowth of its axon, can appropriately regulate its gene expression.

Materials & Methods

Animal Selection & Surgery

The two age groups of animals used in this study were designated as "young adult" and "aged". The age of the younger animals (3 months) represents the time at which early developmental changes have stabilized and the central nervous system has reached adult dimensions, whereas at 23 months the animals are considered to be aged. Three young adult (197±12 g) and 3 aged (395±11 g) male Fischer 344 rats (Harlan Sprague Daw-ley, Indianapolis, IN) were anaesthetized (chloral hydrate, 400 mg/kg intraperitoneally) and the sciatic nerves were crushed bilaterally at the mid-thigh level as previously described[3]. Fourteen days later the rats were killed (chloral hydrate, 800 mg/kg intraperitoneally) and the L4-L5 DRG were removed, weighed, and frozen at -80°C for Northern analysis.

Selection of cDNA Probes

The following probes were used: a 2 kb mouse NF-L cDNA; a 1.1 kb rat GAP-43 cDNA encompassing the full coding region; and a 192 bp MboII fragment of mouse α_1-tubulin cDNA consisting exclusively of the 3' untranslated region. This last region is specific for α_1-tubulin and shows extensive homology among species. The cDNAs were amplified, purified, and labelled using the random priming method with [α-32P]dCTP as previously described[3].

Northern Analysis

Total RNA was isolated using the acid guanidinium thiocyanate-phenol-chloroform method[18]. Gel fractionation and Northern analysis were performed as previously described[3]. Each gel contained RNA for a control and experimental animal from each age group. Three such gels were created, each using RNA from a separate set of animals. Hybridization was performed at high stringency (hybridized at 60°C and washed at 65-70°C with 0.1x standard saline citrate (SSC); 1xSSC = 0.15 M sodium chloride and 0.15 M sodium citrate), and the membranes were exposed to radiographic film for 16-24 hours.

Statistical Analysis

The density and area of specific bands on autoradiograms were quantitated by video densitometry (Bioquant System IV; R & M Biometrics, Inc, Nashville, TN). For each mRNA, the data were normalized to the value of the 3 month control sample on the same autoradiogram. The values for each of the control and experimental animals in both age groups were then respectively averaged. The data were expressed as mean and standard error of the mean (SE), and analyzed with a non-parametric test for comparison of multiple samples (Mood median test) using the Minitab statistics package (Minitab, State College, PA).

Results

The amount of total RNA recovered from the control and axotomized L4-L5 DRG did not differ for the 3 month or 23 month animals (3 month control, 4.62±0.44 μg/DRG; experimental, 4.59±0.16 μg/DRG; 23 month control, 4.69±0.49 μg/DRG; experimental, 4.32±0.19 μg/DRG; Mood median test, $p > 0.05$).

Northern analysis showed marked differences in α_1-tubulin and NF-L mRNA levels between young (3 month) and aged (23 month) control animals; levels in the aged animals were lower by 40% and 60%, respectively. In

contrast, the mRNA levels of GAP-43 were not altered with aging (Figures 1 & 2).

In young adult rats, there was an increase in α_1-tubulin and GAP-43 mRNA levels and a decline in the NF-L mRNA level following axotomy (Figures 1 & 2). This regenerative expression profile was similar to that seen in the aged DRG. Following axotomy in aged rats, α_1-tubulin and GAP-43 mRNA levels were induced to the maximum levels seen in young rats, even though the baseline level of α_1-tubulin began much lower in the aged DRG. The NF-L mRNA levels declined proportionately in aged and young rats after axotomy, despite the fact that the baseline levels were lower in the aged animals. Thus, the final absolute level of NF-L mRNA was lower in aged than young adult axotomized rats.

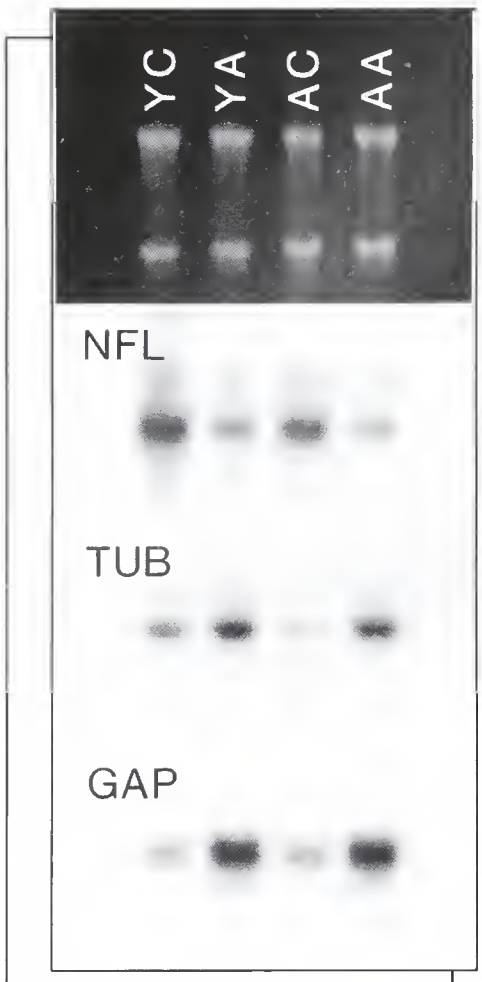


Figure 1: Northern analysis of young adult and aged rat DRG 14 days following axotomy. Top panel: total RNA (5 µg) from young (3 month) control (YC), young axotomized (YA), aged (23 month) control (AC), and aged axotomized (AA) DRG, separated on an agarose/formaldehyde gel with ethidium bromide stain. This gel was sequentially hybridized to α_1-tubulin (TUB, 1.8 kb mRNA), GAP-43 (GAP, 1.4 kb mRNA), and NF-L (NFL, 4.0 and 2.5 kb mRNAs).

Discussion

Axotomy of a mammalian peripheral axon results in degeneration of the distal axon and, in the first regenerative phase, the emergence of regenerating fine-calibre sprouts from the proximal axon stump[1]. The second recognized phase of regeneration consists of the active elongation of daughter axons, followed by the final phase wherein maturation of the newly formed axons occurs by radial growth[1].

An induction of tubulin[2-6] and GAP-43[2,3], and reduction of NF[3,4,8] gene expression have all been shown to occur after peripheral axotomy in developing and adult neurons. Tubulin participates directly in the mechanisms of axonal elongation as microtubules are assembled, transported, and inserted into elongating daughter axons[19]. Neurofilament proteins, on the other hand, assemble into a class of intermediate filaments whose role is believed to be structural; a strong correlation exists between the calibre of an axon and the number of NFs it contains[7]. GAP-43, a predominantly neuronal membrane phosphoprotein, is among the materials enriched in growth cones or presynaptic terminals and is thought necessary for growth cone extension[20].

The present study evaluated the neuronal gene expression of cytoskeletal and membranal components in young adult and aged DRG sensory neurons following axotomy. We have shown that the aged mammalian peripheral neuron can respond to the metabolic challenge that follows axotomy by appropriately regulating the expression of several genes necessary for successful nerve regeneration. In particular, the results indicate that at 14 days post-axotomy, the induced response in aged rats of α_1-tubulin and GAP-43 mRNA levels is identical to that seen in young adults. The degree of decrement in NF-L mRNA levels post-axotomy is also similar between the different age groups, although initial levels are lower in aged animals. These results suggest that although differences may exist in the constitutive expression of these genes with advancing age, the aged neuron is as capable as the young adult neuron in regulating its gene expression following axotomy. Therefore, this ability of aged neurons further suggests that factors other than the control of gene expression must be responsible for the diminished rate of axonal regeneration.

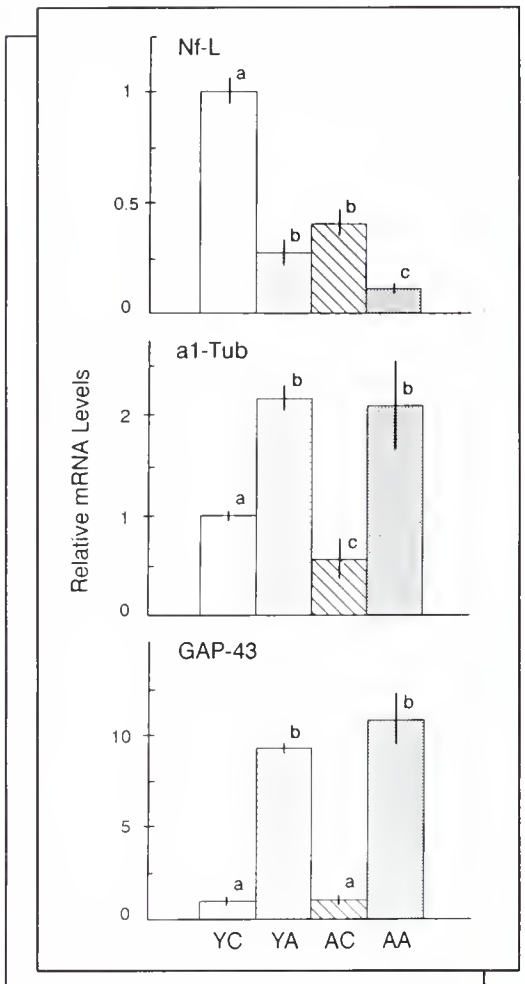


Figure 2: Quantitative Northern analysis of control and axotomized DRG. Autoradiograms of α_1-tubulin, GAP-43, and NF-L were quantitated; the levels for young axotomized (YA), aged control (AC), and aged axotomized (AA) rats were normalized to the young control (YC). The vertical lines are the SE. In each graph, the letters (a-c) express statistical significance (Mood median test, $p < 0.05$) such that values that do not share a letter are significantly different.

Constitutive Decline in Neurofilament and Tubulin Expression With Aging

A number of factors, both intrinsic and extrinsic to the neuron, may be capable of influencing the constitutive level of cytoskeletal gene expression during aging. There

may exist an inability of the aged neuron to access its genome for transcription purposes, resulting in a global down-regulation of gene expression. Changes in chromatin or DNA structure[21,22], diminished levels of RNA polymerase[23], and accumulation of metabolic byproducts[24] (i.e. lipofuscin) have all been shown to occur with aging. Any one of these age-related changes may be capable of interfering with the normal processes of gene transcription, RNA processing, or translation into protein. However, these mechanisms seem unlikely, since while the activity of certain neuronal genes (e.g. NF-L, α_1-tubulin, ß-amyloid precursor protein[25], $GABA_A$ α_1-1-receptor subunit[26]) declines with age, the activity of others (e.g. GAP-43, $GABA_A$ α_1-2-receptor subunit[26]) remains unchanged.

Alternatively, a programmed, senescent decrease in the constitutive level of gene transcription may occur with aging. Part of the process of cell differentiation during development involves down-regulating the expression of genes not required in the mature form. One could then speculate that similar mechanisms of altering gene expression during neuronal maturation may also exist for the aging neuron. Alternatively, other intrinsic properties unique to the aged neuron may be capable of influencing gene expression. For example, the level of depolymerized tubulin subunits within cells has been shown to control the level of tubulin gene expression through a mechanism involving mRNA degradation or destabilization[27]. Differences exist in the pattern and rate of microtubule assembly between young and aged rats, with the aged neurons showing a significant reduction in microtubule assembly[28], and hence an increased pool of depolymerized tubulin.

The level of NF gene expression correlates closely with axonal NF content and axonal calibre, with the increase in postnatal expression occurring as developing axons undergo radial growth towards their mature size[29]. Additional studies from our laboratory have shown that the decrease in NF mRNA levels with aging is associated with a decline in NF protein, axonal NF content, and axonal calibre[30]. The decrease in NF-L may, therefore, represent a primary or secondary component of the pathogenic process involved in axonal atrophy with aging, the exact nature of which remains unresolved.

Although its precise function remains unknown, expression of GAP-43 is increased during development[20], axonal regeneration[2,3], and in regions of the mature brain where synaptic remodelling occurs throughout life[31]. If the loss of neurons triggers the surviving cells to sprout and replace lost connections, then the compensatory mechanisms of growth and remodelling during aging, such as dendritic hypertrophy and synaptic regrowth, may be part of a lifelong program to maintain and adapt brain function. Therefore, in our study, the unchanged level of GAP-43 mRNA with advancing age may simply reflect such a compensatory mechanism.

Diminished Regenerative Rate With Aging

Aged animals require more time to regenerate injured peripheral axons, although re-innervation is eventually as complete as in younger animals[10-12]. Various hypotheses have been put forward to account for this finding, including alterations in mechanical, trophic, and metabolic factors.

(a) Mechanical Factors:

Ultrastructural examination of peripheral nerves shows no evidence that endoneurial cells, matrix, or debris restrict available space within the fascicle with increasing age and, therefore, are not thought capable of limiting axonal growth[12]. Following axotomy, Wallerian degeneration leads to the removal and recycling of axonal and myelin-derived material, and prepares the environment through which regenerating axons grow. In aged rats, there is a delay in the initiation of Schwann cells and macrophages to clear the degenerative debris, although once initiated, the process proceeds at the same rate as in younger rats[12,14].

There are also age-related changes occurring in the axonal transport system[10,32], specifically in the transport velocities of slow components a and b (SC_a and SC_b)[32]. Neurofilament proteins are transported predominantly in the slower moving SC_a, moving at a rate of approximately 1 mm/day, whereas tubulin is present in both SC_a and the slightly faster SC_b which moves at a rate of 2-6 mm/day[19]. The tubulin in SC_b is transported at a velocity equal to the rate of axonal elongation during regeneration, supporting the suggestion that the transport velocity of this cytoskeletal protein may be a limiting factor in the rate of neurite extension[33]. Thus, aged neurons, with their retarded rate of axonal transport, may be expected to exhibit a slower rate of axonal elongation during regenerative periods.

(b) Trophic Factors:

It cannot be discounted that the aged neuron may be perfectly capable of a full and robust response to axon injury, and that the age-related differences detected are attributable to deficiencies in the generation or reception of signals derived from within target cells or supporting cells in the peripheral nerve. The generally accepted model for induction of this regenerative response requires that a terminal or target-derived trophic factor be conveyed via retrograde axonal transport to the cell soma, where it would invoke changes in gene expression. Trophic factors play a key role in development[15] and axonal regeneration in the adult[1] and may, therefore, also be fundamental for the maintenance and repair of the injured or aged neuron. For example, DRG neurons appear dependent on nerve growth factor (NGF) for trophic support, with effects including cell size enlargement, cytoskeletal organization and axonal growth[34].

NGF levels and receptors may significantly decline with aging[35-37], making dependent neuronal systems more vulnerable to insult in old age. Whether such vulnerability could also result in a diminished capacity for neuronal regeneration remains unknown.

(c) Metabolic Factors:

The onset of regeneration is associated with expression of new genes and synthesis of their proteins. In general, the cytoskeletal and GAP mRNAs produced during regeneration are the same as those associated with axonal growth in embryos. The ability of the aged neuron to re-express genes which have been repressed since the end of development is an intriguing concept as it relates to the present study, since a metabolic limitation could account for the differences observed in the regenerative rates between differently aged animals. Intrinsic differences in nuclear and nucleolar size exist between animals of different ages following axotomy, with the changes occurring more gradually and being prolonged in aged animals[16]. Vaughan (1992) has suggested that following a period of normal regenerative capacity in older animals, the metabolic demands may exceed the capacity of the aged neuron[12]. However, taken together, our results clearly demonstrate that after axotomy, the expression profile of several cytoskeletal and membranal genes in aged neurons mimics that seen in the young adult. The present study examined gene expression at only 14 days post-axotomy, a time which corresponds to the approximate midpoint of the regenerative period in this model[3]. Further studies would need to evaluate the gene expression profile over the entire regenerative period to ascertain whether differences exist during the early outgrowth or later stages of axonal regeneration. A second important issue still remaining is whether the induction of tubulin and GAP-43 mRNAs is translated into increased tubulin and GAP-43 protein levels, and subsequently into altered axonal and membranal composition via axonal transport mechanisms where they can directly influence the properties of the axon and growth cone, respectively.

Conclusions

From a medical and purely experimental vantage point, the question of nerve regeneration is of immense consequence. However, there exists in contemporary medicine the realization that in humans, regeneration of diseased and injured peripheral nerves usually remains frustratingly incomplete. Studies which examine the specific cellular processes that enable neural systems to maintain function following injury enhance our ability to understand and possibly, intervene in the capacity of the nervous system to compensate for neural losses with aging. Aged neurons regenerate at a slower rate than young adult neurons, the explanation of which is likely to be complex. However, the present study, which examined the aged neuron's ability to express important growth-associated mRNAs post-axotomy, demonstrated that the ability to regulate neuronal gene expression following axonal injury is maintained with advancing age.

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Polypharmacy in Elderly Palliative Care Patients

Tamarah Kagan (9T5), Edward Gutman, M.D. (8T2), C.C.F.P.*, and Michael Gordon, M.D., F.R.C.P.(C)**

*Physician, Baycrest Centre for Geriatric Care
**Vice President Medical Services, Baycrest Centre for Geriatric Care

Abstract

The purpose of this study was to examine the nature of polypharmacy in patients admitted to the Palliative Care Unit of the Baycrest Centre for Geriatric Care in order to determine if patterns of medication use changed upon admission to and during the stay on the Palliative Care Unit. The unit has a unique population of patients in that they are both elderly and receiving palliative care. A retrospective chart review of 75 consecutive admissions to Baycrest's Palliative Care Unit from May 1991 to December 1992 was performed. The drugs patients were taking immediately before admission, 7 days after admission, and 7 days prior to death were examined and class of drug was recorded. The data showed that the total number of medications prescribed increased significantly over the hospital stay. Significant changes in prescription patterns were also seen within the specific classes of drugs. It can be concluded from the study that there are important changes in the medication needs of elderly palliative patients as disease progresses. Symptoms such as pain, nausea, vomiting, and constipation need to be monitored and treated. Treatments for concurrent illnesses need to be constantly re-evaluated as the patient's disease progresses in order to prevent serious adverse effects.

BEVERLY NASH

Introduction

Several studies have focused on the use of multiple medications, or polypharmacy, in the elderly[1-4]. These studies have shown that "inappropriate medication prescribing"[1] does occur in skilled nursing facilities and that in a significant number of patients, reduction in the number of medications was possible[1,3,4]. Furthermore, recent hospitalization, number and severity of illnesses, increasing age, and female sex were predictors of polypharmacy[1-4]. As the proportion of the population over the age of 65 continues to increase, the causes and adverse effects of polypharmacy in this group of patients are becoming an increasing concern[1,5-8]. However, the patterns of medication use in elderly palliative patients have not been well studied.

The purpose of this study was to examine the nature of polypharmacy in patients admitted to the Palliative Care Unit (PCU) of the Baycrest Centre for Geriatric Care. This is a unique population of patients in that they are both elderly and receiving palliative treatment. Other studies have shown that hospitalization affects the number of drugs used[1,3,4] as well as the categories of drugs prescribed in elderly patients[3,8].

The aim of this study was to determine if patterns of medication use changed in this population upon admission to and during the stay on the PCU. Our initial impressions from working on the PCU were that the number of medications a patient was taking decreased after admission to the unit. Based on this, the use of medications with progression of disease was examined to determine whether clear trends existed.

Methods

A retrospective chart review of 75 consecutive admissions to Baycrest's Palliative Care Unit from May 1991 to December 1992 was performed. The drugs the patients were taking immediately prior to admission, 7 days after admission, and 7 days before death were examined. Only patients who were on the unit for 21 days or more and died on the unit were included in the study. Patients for whom the pre-admission data was not reliable (i.e. poorly recorded) were also excluded. Furthermore, patients who were admitted for reasons other than palliative care (i.e. respite or chronic care) were excluded from the study.

The total number of drugs and the number of drugs within each of the following classes were examined for every patient at each time period: analgesics; gastrointestinal drugs; cardiac drugs; CNS drugs; topical drugs; antimicrobials; respiratory drugs; and miscellaneous drugs. It should be noted that topical drugs which also belonged in other classes were counted in those classes and not in the topical class; for example, topical antimicrobials were counted in the antimicrobial category. Measurement of the number of drugs prescribed while on the unit was based on the PCU physicians' orders.

The data was analyzed for differences between the three time periods within the different classes using a repeated measures ANOVA by the BMDP.2V statistical program. This analysis calculated said differences for each patient and then determined if these differences were significant in the majority of individuals, i.e. in the sample population overall. For data that did not comply with sphericity, a modified probability value was used (Greenhouse-Geisser). Criteria for statistical significance were $p<0.05$. When statistical differences were found, Tukey's test for post-mortem comparisons was used to determine where the differences existed among the time periods.

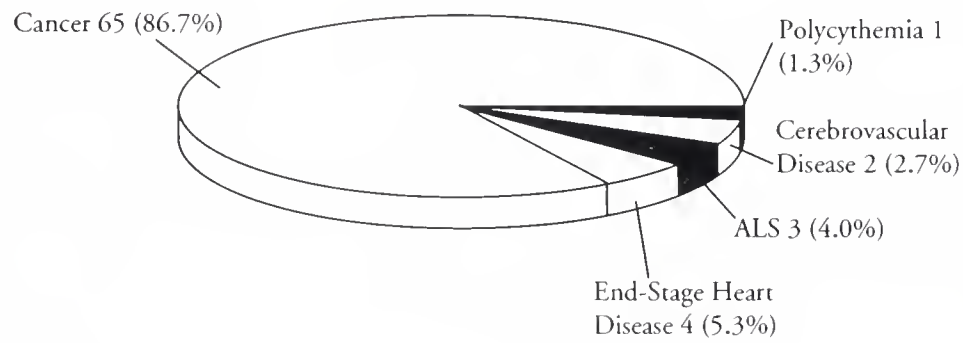
Results

The mean age of the patients studied was 78.3±8.1 years (range 59 to 95 years). Forty-six of the patients were women and 29 were men (female to male ratio was 1.6:1.0). Of the 75 patients studied, 66 were admitted from institutions and 9 were admitted from home. While approximately one-third of all patients admitted to the unit are admitted from home, 23 (72%) of these patients had to be excluded from the study because their pre-admission data was unreliable. Only 2 (3%) of the patients admitted from institutions were excluded for this reason. This likely results from the fact that most patients are discharged from institutions with either a discharge summary or another formal list of the medications they are taking. The mean length of stay on the unit was 80.2±66.5 days (range 21 to 323 days).

The admission diagnoses of the 75 patients are shown in Figure 1. Cancer was by far the most common diagnosis.

The data is summarized in Table 1. It shows a significant increase in the number of medications prescribed during the hospital stay in all classes of drugs except cardiac drugs, antimicrobials, and miscellaneous drugs. There was a significant decrease in the number of cardiac and miscellaneous medications and no significant change in the number of antimicrobial drugs prescribed.

Figure 1



The admission diagnoses of the 75 patients in the study. The number of patients with each diagnosis is indicated.

Discussion

Although our initial impressions from working on the palliative care unit (PCU) were that the number of medications a patient was taking decreased after admission to the unit, the data did not support this. In fact, there was no significant difference in the total number of medications patients were taking in the early stages of their stay on the PCU compared with the pre-admission period. Furthermore, patients tended to be on more medication in total just before death. This is consistent with the finding that polypharmacy is associated with severity of disease[4]. To understand the significance of this, changes in individual classes of drugs over time must be examined.

There was a significant increase in the number of analgesic mediations that patients were taking from the time of admission to the time just prior to death. This proba-

bly reflects progression of disease. Since most of the patients in the study had cancer, it is not surprising that pain was an important issue. Although tolerance to analgesics, especially opioid analgesics, does occur[9], this data does not reflect this as it only shows the number of medications and does not consider dose.

There was a significant increase in the number of gastrointestinal medications prescribed in the first week of the hospital stay. This category of drugs was composed mainly of antiemetics and laxatives. The increase reflects the considerable problems of nausea, vomiting, and bowel regulation in this patient population. These problems have been noted in palliative care patients and are frequently side effect of medications, especially analgesics[10]. These problems were likely treated more aggressively after admission to the unit due to increased levels of monitoring.

The number of cardiac medications prescribed decreased significantly from the time of admission to the time one week later (i.e. from Time1 to Time2). The drugs in this class primarily included diuretics, nitrates, cardiac glycosides, calcium channel blockers, and other antihypertensives. These changes emphasize the need to keep monitoring and re-evaluating the treatment of heart failure, hypertension, and ischemic heart disease in elderly palliative patients. As their oral intake of food and water decreases, they become susceptible to dehydration and hypotension, and as their underlying terminal disease process predominates, prevention of long term complication becomes irrelevant.

The number of CNS medications prescribed, including sedatives, anxiolytics, anticonvulsants, and antidepressants, increased significantly during the latter part of the hospital stay. This may reflect the increased incidence of delirium and anxiety observed on the unit as illness progressed. However it should be noted that studies have found that the use of psychotherapeutic drugs in the elderly tends to increase with hospitalization,[4,8]. This may have been a factor here as well.

The number of topical medications prescribed also increased significantly during the latter part of the hospital stay. This is likely due to the fact that as disease worsens, patients often become increasing bedridden, making them highly susceptible to decubitus ulcers. Furthermore, many patients become incontinent, putting them at risk of developing a diaper rash. Both of these problems were frequently observed on the unit.

The number of respiratory drugs used increased significantly one week before death. This likely reflects the frequency of respiratory complications such as aspiration, pulmonary edema, and accumulation of respiratory secretions that were observed to occur near the terminal phase of illness.

In the miscellaneous category, the number of drugs prescribed decreased significantly in the final stage of the hospital stay. This mainly reflects a reduction in the use of diabetic medication, likely due to decreased oral intake, as well as a reduction in the use of steroids either because the patients were no longer able to swallow or because progression of disease made steroid therapy irrelevant. All of these factors were significant issues on the unit.

It is important to emphasize that this study only reflects changes in the number of medications in each class and does not reflect changes in dosages of medications. This is especially important when considering the analgesic class of medications in which the number of drugs does not reflect the increased need for analgesics that is seen both by increased dosages with time as well as by a change in medication to more powerful analgesics (e.g. from a weak opioid to a strong opioid.)

Table 1
Mean number of drugs taken by patients immediately prior to admission (Time1), one week after admission (Time2), and one week before death (Time3) according to class of drugs.

Class of Drugs	Mean Time1*	Mean Time2*	Mean Time3*	"P" Value**	Times which differ
Total	7.80±4.82	8.56±3.13	9.77±3.66	0.0005	1&3, 2&3
Analgesics	1.01±0.78	1.21±0.50	1.37±0.59	0.0011	1&3
GI	2.52±2.12	3.25±1.77	3.40±1.95	0.0034	1&2, 1&3
Cardiac	1.35±1.77	0.99±1.49	0.85±1.41	0.0006	1&2, 1&3
CNS	0.87±1.12	0.91±0.79	1.15±0.87	0.0213	1&3, 2&3
Topical	0.63±0.97	0.79±0.93	1.29±1.28	<0.0001	1&3, 2&3
Antimicrobials	0.35±0.71	0.45±0.66	0.49±0.67	0.2994	NONE
Respiratory	0.20±0.55	0.23±0.58	0.57±0.86	<0.0001	1&3, 2&3
Miscellaneous	0.88±0.94	0.73±0.70	0.64±0.80	0.0303	1&3

*Mean ± Standard Deviation
**"P" value from the repeated measures ANOVA

Other studies on polypharmacy have shown that institutionalized elderly patients tend to receive more medications than patients in the home[1-3]. In addition, the classes of drugs used often differ between these two settings[8]. This may reflect a difference in severity of disease. However, it has also been shown that factors relating to the institution, such as its size and the type and intensity of nursing care provided, affect prescribing habits[3]. Since so many of the patients admitted from home had to be excluded from our study, there was no way to explore whether admission from home or from institutions affects the data. To explore this factor in this population of patients, a prospective study would have to be done in

which greater attempts would be made to get an accurate list of medications the patients were taking at the time of admission.

Conclusion

It can be concluded from this study that medication needs in elderly palliative patients show significant changes as their disease progresses. Pain increases in many patients over time. It is also imperative to monitor patients for nausea, vomiting, and constipation as these are important and frequent symptoms in this patient population. Furthermore, with progression of terminal illness, the impact of previous diseases on the patient's well-being changes. It is therefore crucial to monitor treatment for these diseases in order to avoid adverse effects such as hypoglycemic attacks from diabetic medications, electrolyte toxicity or dehydration from diuretics, or hypotension from antihypertensive agents. In these patients where symptom control is the primary goal, reassessing and changing medications as needed is essential in maintaining comfort.

Acknowledgements

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Intravenous Drug Use and Needle Sharing Among Toronto Street Youth

Nora Cullen, M.Sc. (9T4) and Sandro Galea (9T4)

Department of Behavioural Sciences, Faculty of Medicine, University of Toronto

PAULETTE DENNIS

Covenant House (CH) in Toronto, it was found that 27% had tried intravenous drugs at least once and 11% were habitual users. Of the 45 individuals who had taken IV drugs, 14 had injected themselves with needles that had previously been used by another drug user; 9 of the 14 either did not clean the needles or cleaned them incorrectly. Ten of the users had given their needles, without cleaning them first, to others for reuse. Thus, at least 19 young people were placed at high risk of contracting HIV. These data suggest that there is a need for increased education of the youth about the dangers that they are exposing themselves to, and for greater accessibility to clean needles in Toronto.

Abstract

The sharing of intravenous needles has been shown to be a factor in 15% of HIV cases. In order to curtail this outbreak, there has been considerable effort on the part of health care workers dealing with Toronto's street youth to provide education about the dangers of sharing needles. In spite of these efforts, there remains a significant proportion of young people who are still using intravenous drugs in a high risk manner. In a study of 168 runaway youths conducted at

Introduction

The use of contaminated needles for drug injection has been shown to be an efficient means of transmission of many blood-borne infections including HIV, hepatitis, malaria, and bacterial endocarditis[1,2,3]. Intravenous (IV) drug use accounts for up to 20% of HIV-positive cases in 13 to 23 year olds in the United States[4]. The dangers of sharing needles with someone who has been infected with a blood-borne disease is a reality that health care workers are still seeing the ravages of, in spite of the valiant effort of many agencies. Although most of the

young people are aware of this risk, the scarcity of needles, combined with social and cultural factors, generates dangerous sharing practices.

In Toronto, there are several places where youths can go to obtain sterile injecting equipment at no cost to themselves. These include The Works, SOS, and Inner City/ Youth Link, among others. This study was designed to determine whether or not young adults who use IV drugs are being adequately reached by existing programs to prevent HIV infection and if there is a demonstrated need for CH, a crisis centre for street youth, to operate another such programme.

Table 1
The number of times IV drug users surveyed (n=45) have tried IV drugs.

Times IV drugs tried	Number of young people	Percent of total
Once	9	20
2-10	10	22
10-100	7	16
>100	19	42

Methods

The surveys were conducted at three locations associated with CH: Health Care Service, a walk-in clinic servicing health needs of street youth; 100 Bond Street, the CH community outreach program; and The Van, a vehicle which moves around the city assisting street youth who are in need of emergency services.

The survey sample consisted of 168 young people aged 16 to 21, of which 120 were males and 39 were females, who had visited CH or The Van between June and August of 1991. They were informed of the nature of the survey; confidentiality, informed consent, and the voluntary nature of answers to questions were emphasized. A standardized questionnaire was given to the youth who agreed to participate. To avoid recording inconsistencies, it was administered by the authors in all cases.

Questions were asked regarding the total length of time spent on the street, places lived in other than the street, the duration of the latest episode on the street, and the highest level of education attained. The number of times respondents had injected IV drugs was determined, along with who they were usually with when using drugs, reasons for drug use, types of drugs injected, and where the drugs and needles were obtained.

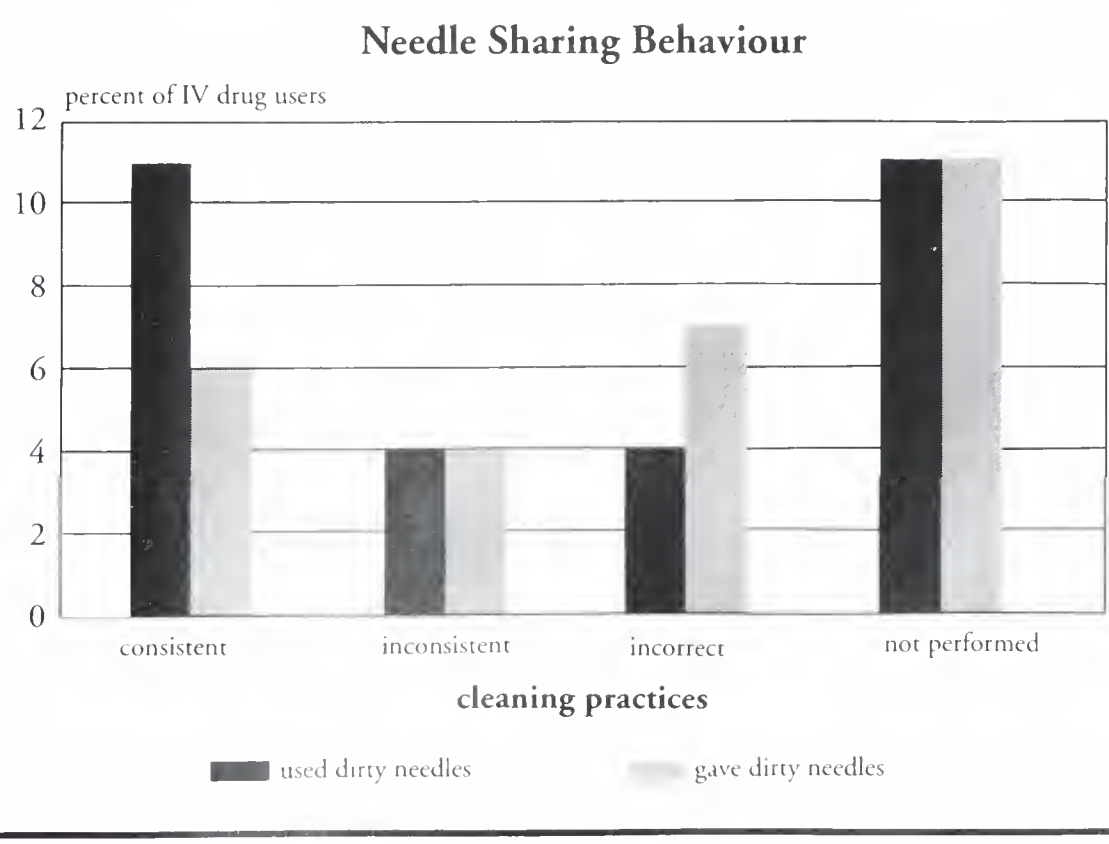
In order to assess the general level of knowledge about the dangers inherent in IV drug use, all of the youths surveyed were asked what diseases they knew of that could be contracted by sharing needles. They were also asked where they could obtain clean needles and how they would clean a needle if they were ever in a situation where they or their friends needed clean needles quickly.

Results

Among the youths surveyed, the average respondent had first come to live on the street 35 months ago (range: 1 day to 12 years). While 64% had lived in places other than the street since first leaving home (e.g. apartments, motels, with friends), 36% had stayed on the street the entire time. The average length of the most recent episode on the street was 10 months. The mean level of education achieved was grade 10.

Twenty-seven percent of those interviewed had used IV drugs at least once and 60 (36%) had friends who used IV drugs regularly. In 11%, one or both parents were habitual users. Frequency of IV drug use is summarized in Table 1.

Figure 1
Needle sharing behaviour among users. The percent of users who cleaned their needles correctly each time, not always, not correctly, and not at all is shown by the dark bars. Those who gave their used needles to others are divided similarly (hatched bars).

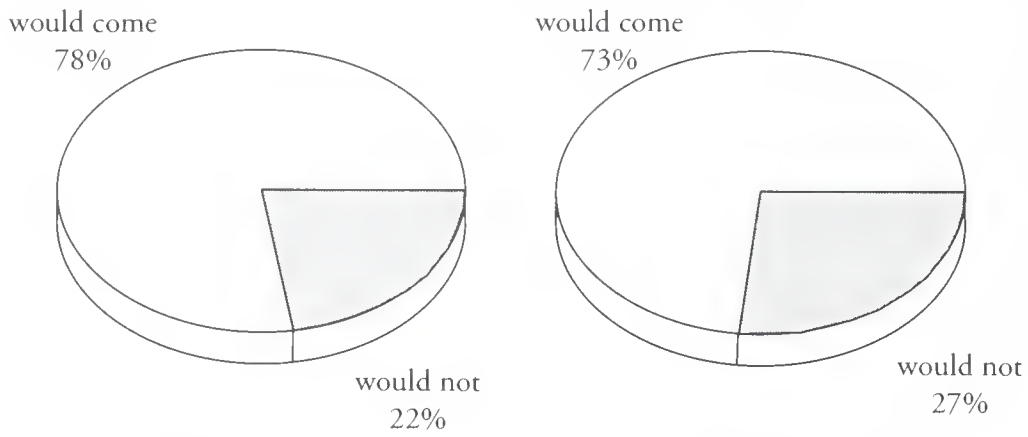


The most common reason given for using IV drugs (45%) was that it provided a "better high" compared with other routes of administration. Other reasons cited included peer pressure (26%) and curiosity (26%). The average time since last using IV drugs prior to the survey was 16 months (range: 1 day to 6 years). Three of the 45 users took drugs when alone, 31 did so with friends, and 10 used drugs both alone and with others; our youth did not respond to this question. Thirty-three had used cocaine and 18 had tried various other drugs intravenously.

Drugs were obtained from dealers (54%), friends (41%), or family members (4%). Needles were acquired from drugstores and hospitals (18 of 45 cases), friends or family members (14), The Works (9), SOS (6), Inner City Youth Link (5), or dealers (2).

Of the 45 youths who had tried IV drugs, 14 had reused a needle. Five of this group did not clean the needles before they injected the drug and 2 cleaned them inconsistently.

Figure 2
Percentage of users who stated that they would utilize the services of a needle exchange at Covenant House or on the street outreach.



Of the 7 that did clean their needles prior to use, 2 were cleaning them incorrectly. Thus, there were 9 youths in this group who placed themselves at high risk for contracting HIV from needles that had been previously used and not cleaned. This represents 5.3% of the total number of street youths that were interviewed in this study. Furthermore, 13 of those who had tried IV drugs had given their used needle to someone else. Of this 13, 5 did not attempt to clean needles, 2 cleaned them inconsistently and [illegible] did not clean them correctly, putting another [illegible] at high risk for contracting HIV and other blood borne diseases. These results are summarized in Figure 1.

The main reason cited for sharing needles was expediency (73%); the urgent need for the drug felt at the time of sharing needles was greater than the fear of contracting a disease. Other reasons included the belief that others did not have the AIDS virus (20%); one individual stated that it was just his own "stupidity".

Most of the users of IV drugs knew of several places where they could obtain clean needles, including Inner City Youth Link, SOS, The Works, drugstores, hospitals, doctors' offices, the Hassle Free Clinic, and Mercury Youth Substance Abuse program. Forty percent had actually used these places to obtain clean needles; the remaining 60% had obtained their needles from other sources such as dealers or friends.

The results of the survey indicated that 4% of the youth did not know of any dangers associated with the sharing of needles, while 90% knew that contracting AIDS was a possibility. Only 18% stated that hepatitis was a disease associated with IV drug use. Twenty-three percent did not know of a place where clean needles could be obtained, while 77% correctly identified one or more locations in Toronto that would provide them with clean needles. Only 39% of the youths knew that used needles should be irrigated with bleach alternating with water two to three times. Twenty-four percent thought that they should rinse with bleach and water only once or use only alcohol or water. The remainder had no idea about how to clean a used needle (36%).

When asked whether they would come to CH in order to obtain clean needles if there was a needle exchange program there, 78% of users said that they would utilize CH's Health Care Service and 73% stated that they would come to the Van for this purpose. The remainder said that they would not come to CH for needles, mainly because they would not want the staff to know that they were using IV drugs. These results are shown in Figure 2.

All of the young people surveyed were asked whether or not they felt that a needle exchange at CH was a good idea. Of the non-users, 79% thought that the programme would be useful at the Health Care Service, and 84% felt that the Van would be an appropriate place for a needle exchange. Twelve youth (9.7% of non-users) stated that they would not like to see a programme such as this at CH because they would not want the staff to know if they were using IV drugs. Another 3 youth felt that the needles would be unreliable with respect to cleanliness, one thought that drug addicts should not have the encouragement to continue with their bad habits, and another felt that the Van location was too unpredictable.

Discussion

This study shows that more than one quarter of street youths surveyed have used IV drugs at least once and 8.3% have used needles that were previously used. This represents a substantial number of youths that have not heard or are not heeding the warnings being put out by health care workers. Over one third of the youths still do not know how to clean a used needle and one quarter do not know where to get clean needles. These data have ominous implications and support the need for implementation of a needle exchange programme at CH and other places. According to the youths who have used needles, the majority (78%) would utilize such a programme; as well, most of the non-users surveyed supported this idea.

Since there are some young people who do not realize that AIDS is a danger of needle sharing and 82% of those surveyed did not know that hepatitis can be contracted by sharing needles, there is a need for increased effort in education of youth in the dangers associated with needle sharing.

It appears from the results of this study that those sharing needles are either ignorant of the dangers to which they are exposing themselves, do not know where to obtain clean needles, or simply share needles for the sake of expediency no matter how educated they are about the dangers or how easily obtainable the needles are. The last group exclude themselves from receiving assistance at this stage in their lives. However, the groups who do not know where to obtain clean needles or do not know of the dangers associated with the sharing of needles are good candidates for receiving the kind of assistance that a needle exchange programme might bring. Since these youths are in contact with CH, this would appear to be a logical place to provide clean syringes along with a programme designed to educate youth about of the dangers associated with the sharing of intravenous needles.

It may be said that bad habits are being encouraged by offering the vehicle of drug abuse for free. On the other hand, it can be argued that the increased availability of clean needles may keep young people alive longer so that they can be assisted at a future date when they are more adequately prepared to give up the use of the drugs.

Some of the youths raised the question of credibility in regard to both the reliability of the clean needle programme and their own status with staff as they did not want them to know that they were using the drugs. This may indicate that while a rapport has been established, work needs to be done in further enhancing a trusting relationship between the youths and the staff.

Conclusion

The desire to stem the tide of the spread of HIV must be tempered with realism. While young people are largely cognizant of the dangers associated with sharing needles, the reality is that unless the equipment is readily available to users at the time that they want to inject, they will continue to share with peers. Although it would be ideal to achieve the cessation of all drug abuse, this is an illusory goal at this time. Until such time as IV drug users are ready to give up their habit, avoidance of the consequences of shared needles is a realistic goal that will help to minimize the spread of HIV and other diseases.

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The Gairdner Foundation 1993 International Awards

D'Arcy Little (9T5), Toronto, October 1993.

In his opening remarks, Dr. Charles Hollenberg, the President of the Gairdner Foundation, described the Gairdner Foundation International Awards as a festival which brings together a group of the most outstanding medical scientists in the world. This year, five such scientists, all from the United States, each received awards of $30,000 (Can.) and presented a lecture series held in the J. J. R. Macleod Auditorium at the University of Toronto on October 21st and 22nd.

Dr. Mario R. Capecchi

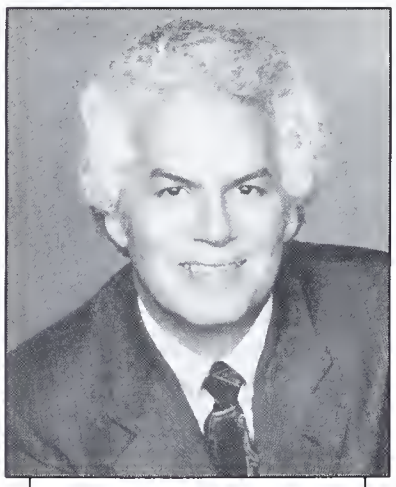
Dr. Mario R. Capecchi of the University of Utah in Salt Lake City, and Dr. Oliver Smithies of the University of North Carolina at Chapel Hill, were recognized jointly for their independent creation of a gene targeting technique. The importance of this technique lies in the fact that it allows the "knock-out" or disabling of a single gene in a living mouse. Since hu-mans and mice share approximately 90% of their genes, these "knock-out" mice can serve as useful laboratory models of human diseases, and as such allow the testing of drugs and gene therapies. They have so far been applied to such genetic diseases as cystic fibrosis and ß- thalassemia and have also been used to study embryonic development, immune deficiency, memory defects, and tumour development.

Dr. Oliver Smithies

The artificial production of mutations in mice has traditionally been a random process. Dr. Capecchi and Dr. Smithies, however, realized that homologous recombination could be made to occur at a significant frequency by introducing into cells DNA identical to a gene in the host but containing a specific mutation to disrupt the production of the protein product. Dr. Smithies was the first to demonstrate, in 1985, that a normal mammalian gene could be altered by homologous recombination in human cells in culture. This knowledge was then applied by Dr. Capecchi to introduce mutations into mouse embryonic stem cells which have the ability to contribute to all tissues in the mouse, including the mouse germline, when they are returned to an early embryo. This allowed him to enrich the homologous recombinations seen against a background of random genetic events and to select the recombinations with a positive-negative selection system that he also developed. In addition, Dr. Smithies initiated the use of the polymerase chain reaction to identify the homologous recombination events. As a result of homologous recombination in embryonic stem cells, Dr. Smithies was one of the first to produce mice carrying a targeted mutation in a specific gene.

Dr. Alvan R. Feinstein

Dr. Alvan R. Feinstein of the Yale University School of Medicine was honoured for his contributions to clinical epidemiology. He is recognized internationally as a leader in establishing modern clinical epidemiology as a scientific discipline for the study of the causes, diagnoses, prognoses, and therapies of disease. His principles and methodology have led to improved classification of disease and to the quantitative use of clinical signs and symptoms in the study of disease. For instance, his work has contributed to the prevention of rheumatic fever and to the improvement of cancer prognosis assessment. Dr. Feinstein has also played a great role in medical education. He has written classic texts on clinical epidemiology, and as director since 1974 of the Robert Wood Johnson Clinical Scholars Program at Yale University, has trained over one hundred graduates who now occupy leadership positions in North American academic medicine.



Dr. Stanley Prusiner

Dr. Stanley Prusiner of the University of California at San Francisco was recognized for his formidable contribution to the understanding of brain degeneration caused by novel infectious agents called prions. Prions are proteinaceous particles which, unlike bacteria, viruses, or fungi, are infectious even though they have not been found to possess any nucleic acids. Prions are associated with human

and animal diseases that cause mental retardation and death and which were previously considered to be degenerative in nature. For example, prions have been found to be responsible for uncommon neurological diseases such as Creutzfeldt-Jacob disease, kuru, and Gerstmann-Straussler-Scheinker Syndrome, as well as more common diseases in cattle and sheep (mad cow disease and scrapie, respectively). For a model, Dr. Prusiner has recreated human brain disease in mice by transmitting these infectious agents. It has been learned that the precursor of prion protein is produced by a gene normally found in all mammals which, when altered, becomes infectious and causes the accumulation of abnormal protein and consequently the death of brain cells. A slowly progressive degeneration of the brain proceeds to loss of memory, impaired intellect, paralysis and even death.

Finally, Dr. Michel Ter-Pogossian of the Washington University School of Medicine was recognized for the invention and development of the positron emission tomographic (PET) scanner. This scanner represents a special form of imaging technology; unlike other imaging modalities that show structure, the PET visualizes metabolic and biochemical activity. Short half-life radioactively-labelled chemical compounds produced in a cyclotron are inhaled or injected into the body and then send out gamma rays when they have arrived at specific target sites. These rays are picked up by a circular array of crystal detectors and turned into images via computer technology. The technique can be used to study any organ of the body, but has been most useful in the study of brain function. The PET scanner is a productive research tool. Although there are only 100 PET scanners in existence, including four in Canada, 10% of all scientific publications in the neuroscience field are associated with PET studies.

Dr. Michel M. Ter-Pogossian

The Gairdner Foundation, established in 1957 by the late James A. Gairdner, has honoured 230 scientists, 43 of whom have gone on to receive a Nobel Prize. Mr. Gairdner was born in Toronto in 1893. He served in the Canadian army in World War I but retired from the forces in 1918 as a Major to begin a successful career as a stockbroker and industrialist. At the age of 56, after suffering a severe attack of arthritis, he took up oil painting. In fact, Gairlock Gardens in Oakville, the place where he lived and painted, is now an art gallery and public park.

Throughout his life, James Gairdner showed a practical interest in clinical medicine and medical research. He also believed strongly that the accomplishments of medical scientists should be recognized, so with the encouragement of Dr. Wallace Graham, a leading rheumatologist in Toronto, he established the Gairdner Foundation International Awards. Originally, these awards were confined to the fields of arthritis, rheumatism and heart disease. More recently, the awards have been extended to include other areas of medicine such as immunology and molecular biology. Although Mr. Gairdner died in 1971, outstanding medical scientists continue to be honoured each year in his name.

I am thankful to Ms. Sally-Anne Hrica, Executive Director of the Gairdner Foundation, for much of the above information and for the photographs.

TRAINING IN RADIATION ONCOLOGY

The Princess Margaret Hospital and the Toronto-Bayview Regional Cancer Centre combine forces to provide training in all aspects of managing cancer patients, with an emphasis on radiotherapeutics. This specialty combines broad clinical skills with high tech radiotherapy treatment planning and delivery systems.

An exciting future awaits those who take up this challenge, both in the treatment of individual patients and in pursuit of clinical and laboratory investigations.

FOR FURTHER INFORMATION:

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Dr. Woodrow Wells
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Telephone: 924-0671 ext 5443

Health Care for the Street Kids of Toronto

Vincent Ho (9T5)

Why the street youth?

One of the most underserviced and overlooked populations in health care is the 10,000 street youth of Toronto. They are teenagers who have run away from home or have been kicked out of their homes. The majority have left situations so abusive that the street offered a better life. Their health needs are often overlooked; they have very limited access to the health care system, lacking health cards, drug benefit plans, and often, legal identification. In addition, the abuse that drove them to the streets in the first place may have bred fear and distrust of the system, preventing them from seeking the help they need from established medical services.

Who is Evergreen and what are they doing?

Yonge Street Mission, founded in 1896, is a non-profit interdenominational Christian organization dedicated to sharing God's love in practical ways with the poor and needy of downtown Toronto. Evergreen, Yonge Street Mission's centre for street youth, has recently renovated part of its basement into a modern walk-in Health Centre. Evergreen aims to be a family and home for the street youth, a place of safety, dignity, and friendship. With the opening of the Health Centre on January 24, 1994, it is hoped that the health needs of the street youth will be met in their own "home", where youth can be treated with compassion and dignity by health professionals.

The Health Centre has three rooms which are fully equipped for offering medical, dental, and ophthalmological services. There is also a small lab for simple tests and a classroom for primary health education. The Health Centre will be open at the same time as the drop-in: Monday to Friday from 1:00 to 4:30 pm. All services and medications will be offered to the street kids free of charge. More than just being a place that provides free health care, the Health Centre is meant to be a place where street kids can learn how to live a healthy lifestyle.

How can YOU partner with Evergreen?

Medical students at the University of Toronto performed research in conjunction with Evergreen in 1989 and determined that the health needs of street youth were similar to that of a third world population. Again, the invitation is open for students, alumni and friends of the University of Toronto, particularly those who are health professionals, to be partners with Evergreen in the free health care of street youth. Dentists are also needed. Evergreen is looking for people who are patient, kind, trustworthy, non-judgmental, open-minded, and devoted to providing a high standard of health care to some very needy people. They are asking for a minimum volunteer commitment of one afternoon per month. Evergreen also needs clinical and pharmaceutical supplies; already one laboratory in the city has offered to perform all lab work free of charge. If you cannot help on-site, there are other ways to become involved.

If you are a physician, dentist, R.N., dental hygienist or assistant, or if you are interested in being involved in any way, please contact Evergreen for more information at (416) 977-7259 or write to: The Evergreen Health Centre, 381 Yonge Street, Toronto, Ontario M5B1S1.

They're sick and tired.

Help us care for street kids.

At Evergreen, our centre for street youth, we know a lot of sick kids. But most are unable to gain access to health care because they don't have a health card and can't get one.

Our new walk-in health centre will help meet the need. We're looking for compassionate health care professionals who will volunteer their services so we can provide medical, dental, and eye care, as well as primary health education. For free. No health card required.

Yonge Street Mission

Interested in helping?
Please call or write:

Evergreen Health Centre
381 Yonge Street
Toronto M5B 1S1
(416) 977-7259

Report from India: A Summer at an Outreach Clinic in Sundernagri

Navdeep Nijhawan

The plane landed three hours late on the simmering tarmac of Indira Gandhi International Airport in New Delhi, India. It was 5:30 a.m. and I was exhausted from the twenty-one hour flight. Stepping off the plane, one is immediately overcome by the intense 35°C heat which makes a person's skin feel as if it's being stabbed by millions of pins and needles. It would take days to get used to the heat.

My accommodations were located in the dormitory of St. Stephen's Hospital, a privately-run Christian hospital in the heart of old Delhi. Since my supervisor was the hospital director, I had expected to spend most of my time there, but he suggested that I spend my first two weeks in the hospital's outreach clinic in the slums. Although hesitant at first, believing I would not be able to complete my intended project, I agreed. To my amazement, I was so fascinated by the slum areas that I spent my entire summer at the outreach clinic and never once set foot in the wards of St. Stephen's Hospital.

The slum area was located approximately 10 km from St. Stephen's. Each morning, I boarded a private bus with physicians, nurses, and health care workers that took us across the Yamuna river to the urban slum known as Sundernagri. The forty minute bus trip was an experience in itself. The driver's "kamikaze" style, considered quite normal for Delhi, took some getting used to. It was a daily event to see the driver swerve in and out of traffic as he blared his horn to warn the oncoming swarms of bicycles, three-wheeled rickshaws, scooters, and buses. The streets to the clinic were barely wide enough for the bus to pass through. They were overflowing with people busy with their daily activities, young children running around, fruit vendors selling their produce, and sheep and cattle grazing on mounds of hay and grass.

Sundernagri, which literally means beautiful town, is anything but. It is a resettlement colony that is divided into 14 blocks and has a population of approximately 50,000. The inhabitants have migrated to this town from neighbouring states such as Uttar Pradesh. Most of the people are semiskilled or unskilled, have little or no education and work for petty wages. In recent years, the area around the health centre has developed into a weaver's colony and the men and women are actively involved in weaving for large companies. It is interesting to note that almost 40% of the population of this area is Muslim, a number significantly higher than the country's average.

The clinic itself was located within the centre of Sundernagri in a two-storey building. The ground floor contained the clinic facilities, a pharmacy, and a laboratory. There was also a kitchen, a field room where health care workers could update their records, a classroom, and an

office for the coordinator of the clinic. The clinic facilities had the bare necessities: one bed, an autoclave, stainless steel syringes that were reused after sterilizing, three blood pressure cuffs (only one ever worked while I was there), a flashlight, a weighing machine, and several Salter scales.

Located within the clinic was a crèche for children of mothers who worked outside of the home. This crèche had about 40 nursery-aged children and enabled children of the same age to interact with each other instead of staying at home alone or with older siblings while their parents went to work. This set-up had several advantages. Firstly, it allowed older children the opportunity to go to school instead of baby-sitting their younger siblings, allowed mothers to increase the income of their household, and finally, provided the crèche children with an opportunity to learn to read and write.

The clinic provides services to all residents of the Sundernagri area, regardless of religious affiliation, for a nominal fee of 2 rupees. In many instances this fee was waived and at the end of the day it came as no surprise that our money box had considerably less money than we were owed. There were numerous services provided by the clinic including home visits by health care workers. General clinics were held every Monday and Thursday, antenatal clinics every Wednesday, and well-baby clinics every Friday. Special tuberculosis clinics were held on Tuesday and Saturday; tuberculosis is a big problem in the area. In addition, every Friday children were immunized with basic vaccines, including measles, mumps, rubella, and BCG. The clinic's immunization practices were quite successful with a high rate of coverage among children up to age five.

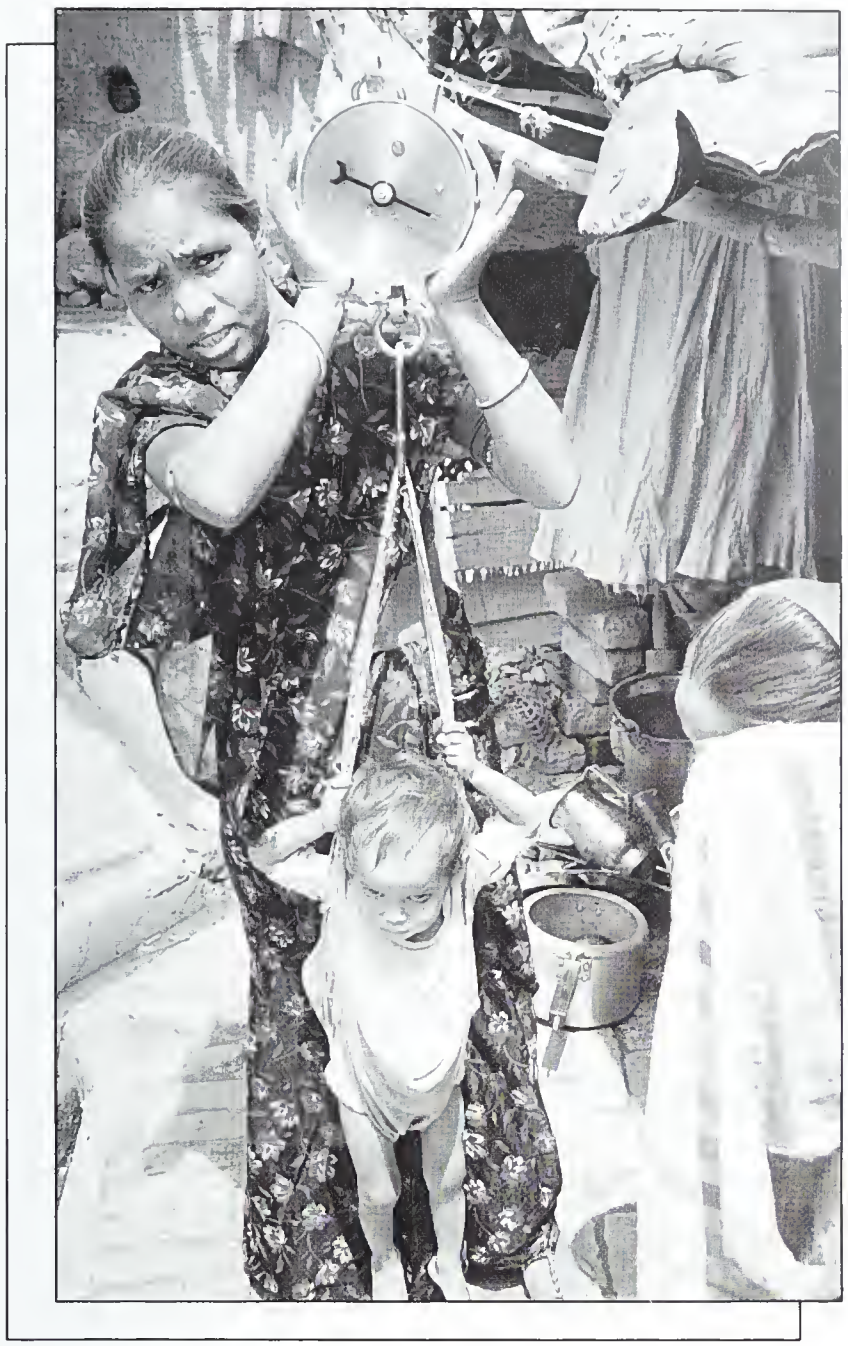
On a typical general clinic day, the coordinator, another staff doctor and myself would see 130-140 patients, which didn't leave too much time for complete histories or physical examinations. I was truly impressed with the amount of information that the doctors were able to obtain and the efficiency with which they worked.

The clinic pharmacy contained only basic medicines such as aspirin, paracetamol, and ampicillin. There were days when we worked without running water or electricity in 45°C heat. The clinic had a generator for such emergencies but it had limited capacity and it was always amusing to see the doctors, nurses, and health care workers huddled around a single ceiling fan trying to get some cool air.

The clinic was in direct competition with local business people who sold tonics and cure-alls that often left the patient worse off because the treatment was ineffective and it delayed the time before they sought proper medical attention. What was interesting was that many of these individuals would charge exorbitant amounts for their treatments which the people were willing to pay, yet when they came to see us they would often ask us to waive the 2 rupee fee.

The majority of the complaints on general clinic days were minor, such as respiratory tract infections, infectious diarrhea, dehydration and malnutrition in children, and skin conditions such as scabies and boils. For more complicated cases the patients were referred to the nearby government hospital or were immediately transported by bus to St. Stephen's Hospital.

During the antenatal clinics I helped obtained mothers' weights and heights, measured blood pressure, and measured fundal height and fetal heart rate. In addition, maternal urine was monitored for protein and glucose in a shoebox-sized laboratory. Obviously, only rudimentary obstetrical care could be given here, and without the aid of ultrasound machines, amniocentesis and other devices, the doctors had to rely heavily on experience and instinct.



In addition to providing obstetrical care, the workers at Sundernagri were actively campaigning to promote contraception. One of India's greatest health concerns is its ever-expanding population; at its current growth rate, India will have over 1 billion people by the end of the decade. In addition, the majority of children will be born to the poorest class as they in large part have refused birth control while the middle and rich classes have embraced it. Acceptance of proven birth control methods such as vasectomies, laparoscopic tubal ligation, and IUDs is very low among people in this community and currently only about 10% of couples targeted for family planning practise a proven form of birth control. Men in the community refuse to undergo vasectomies because they believe this would weaken them to the point where they could not work. Interestingly, many of the wives agree with this theory. Thus, the clinic focuses more on convincing women with two or more children to undergo laparoscopic tubal ligation or insertion of IUDs. It was especially disheartening to note that there is limited success with the program even though the procedures are free of cost and the Indian government actually pays men and women to undergo these procedures.

One of the most disturbing experiences of the summer occurred in early July when representatives from the Canadian and British Embassies came to visit the clinic. They had brought boxloads of medicines to donate to the clinic. We were very excited about this as our drug budget was quite limited. At first I felt extremely proud of the fact that the Canadian embassy had donated these medicines and I made sure everyone knew this fact. Unfortunately my pride was short-lived. As we eagerly unpacked the medicines from the boxes and began reading the labels, we soon realized that the majority of them had expired or would expire by the end of the month. In fact, out of the 6 or 7 boxes that had been donated, we only managed to salvage a few bottles of aspirin, vitamin C, and skin ointments. The clinic workers were extremely upset and wondered why people thought that medicine unfit for human consumption in the West would be fit here. We wrote letters to the Canadian and British embassies but had not received any reply as of the day I left for Canada.

Although I spent the great majority of my time working in a slum area, I did have an opportunity to travel. Wherever I went I was welcomed with open arms. People were always offering what little they had without expecting anything in return. India is a country of extremes. India's wealth is of such magnitude that the opulence of the West pales in comparison. Unfortunately, the majority of this wealth is held by an infinitesimally small number of people. What India (and the West) need to realize is that they must find ways of spreading this wealth among more people.

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BOOK REVIEWS

Sun Damaged Skin

Ronald Marks.
70 pp., Martin Dunitz, 1992.

Ronald Marks, a well known dermatologist from the United Kingdom, has written one of the few books, if not the only one, to deal exclusively with the subject of sun damage to the skin. Sun Damaged Skin is a 70 page collection of text, clinical photographs, and histological illustrations that educate the reader about a topic of serious medical concern. Skin cancer is not only of great significance to dermatologists; family practitioners will encounter many patients with suspicious skin lesions as well.

This book is divided into five chapters. The opening chapter, "Solar Radiation and Susceptibility", discusses subjects such as UV terminology, risk factors for the development of skin lesions, xeroderma pigmentosum, and solar keratoses. In addition, a good histological illustration of the morphological changes to the skin as a result of sun exposure is presented. Chapter two, "Aging and Photodamage", vividly illustrates the deleterious cosmetic effects of sun exposure to the skin. Numerous clinical photographs and histological sections provide effective examples of elastotic degenerative change including wrinkling, telangiectasia, purpura, and scarring. Chapter three, "Skin Cancer", presents the more serious consequences of excessive sun exposure, namely solar keratoses, squamous cell and basal cell carcinomas, and malignant melanoma. The text outlines a clear diagnostic strategy for these lesions. The fourth chapter, "Protection from the Sun", provides practical information concerning prevention of skin disease by means of a comprehensive discussion of sunscreens and their efficacy. A realistic approach to behaviour modification is presented as well. The final chapter, "Treatments for Photodamage", briefly describes therapeutic options including topical retinoic acid and chemical peels. However, the latest medical, surgical and laser therapies are not discussed in great detail. This part of the text could be more inclusive and up to date.

Overall, Sun Damaged Skin is very readable and informative. The clinical photographs provide poignant examples of sun-induced skin pathology. The concise text provides valuable insight regarding pathogenesis, recognition, and management of sun induced skin disease. Many dermatological atlases available to medical students are more comprehensive and describe skin pathology in more detail; however, these atlases tend to focus solely on etiology, pathogenesis, and diagnosis. In addition to covering these three areas, Sun Damaged Skin emphasizes prevention and patient education. It is the obligation of the physician to educate his or her patients about the dangers of excessive sun exposure; the insight gained from this text may enable the physician to do so in a more effective manner.

Paul Cohen, B.A. (9T5)

Basic Gynecology and Obstetrics

Norman F. Gant and F. Gary Cunningham.
472 pp., Appleton & Lange., 1993.

Most book reviews, even critical ones, begin with a few plaudits. Unfortunately, the Gant and Cunningham book is poorly organized, neglects important topics, and is riddled with outdated misinformation. The only mitigating factor is its reasonable price, but given its shortcomings, the book could hardly be considered cheap at any price.

From the reader's point of view, the book is frustrating because the information presented is disorganized, fragmented and hard to find. There are also curious gaps. For example,there is no listing in the index under "pelvic inflammatory disease" and no general discussion of this important topic in the text. Rather, there are brief snippets on PID scattered throughout the book: mentions of salpingitis as a possible complication of infection with *N. gonorrhea* or *Chlamydia trachomatis* in the chapter on STDs, a chapter which fails to discuss HPV infection at all; references to PID in the chapter on Chronic Pelvic Pain; and two paragraphs in the "Family Planning" chapter.

The sections of the book dealing with obstetrics are no better: for example, nowhere in the book is there a comprehensive discussion of risk factors in pregnancy. Instead, the information is scattered between Chapter 36, "Maternal Adaptations to Pregnancy", Chapter 42, "Prenatal Care" (which inexpicably follows chapters on labour, the newborn infant, and the puerperium) and Chapter 54, "Congenital Malformation & Inherited Disorders".

As frustrating as all this is, what is most infuriating about this book is its high-tech, invasive and outdated approach to obstetrics. This may be useful for those who plan to move south (the authors are from Dallas), but it does not reflect the ideal (and, one hopes, the reality) of obstetrical practice in Canada in 1993. Among other things, the book advocates the routine use of enemas, intravenous infusions, narcotics and tranquilizers (promethazine), and episiotomies during normal labour. There is curiously little discussion of the psychology of pregnancy and what there is is trivialized. For example, there is no mention at all of the emotional impact of abortion and the one paragraph discussion of "postpartum blues" ascribes these to "fears that she (the mother) has become less attractive". The role of physiological changes, such as hormonal alterations, and social factors, such as the isolation of new mothers, are completely ignored.

Also offensive is the book's underlying social and moral agenda. The text suggests that sex between married couples is the norm: for example, one heading in the chapter on Sexuality reads "Sexual Function in Marriage and Similar Intimate Relationships". If unmarried lovers are suspect, lesbian or bisexual women are beyond the pale: the suggested format for sexual history taking assumes that the woman's partner is male and the health care needs of lesbian women are totally ignored.

Finally, the book pathologizes normal aspects of women's lives. Post-menopausal women naturally have lower levels of estrogen than menstruating women, but Gant and Cunningham describe this normal state as if it were a disease: "Currently, estrogen therapy is recommended for all estrogen-deficient women unless there is some contraindication". One might, with equal justification, describe all men as "estrogen-deficient" (after all, they too are at increased risk of cardiovascular disease).

In fairness to Gant and Cunningham, many of these same criticisms could be made of other obstetrical and gynecological textbooks. Surely it is time for a more enlightened treatment of the subject, one which accurately reflects the current practice of obstetrics in Canada, as well as the social milieu of the nineties. We need an Our Bodies, Ourselves for physicians.

Rachelle Sender Beauchamp, Ph.D (9T5)

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The University of Toronto Medical Journal

VOL. I FEBRUARY, 1924 No. 3

THE DISCOVERY AND PREPARATION OF INSULIN

F. G. BANTING and C. H. BEST.

There have been numerous reviews of the literature which deals with attempts to prepare potent pancreatic extracts for the treatment of experimental or clinical diabetes. The representative of this journal assures us, however, that it is advisable to refresh the memories of the students of the University of Toronto by brief references to some of the earlier work in this field.

Previous to the year 1889 several investigators had suggested a connection between the pancreas and the disease, diabetes. In that year von Mering and Minkowski proved very conclusively that the complete removal of the pancreas from dogs and other animals resulted in the production of very marked diabetes.

In the year 1869, Paul Langerhans had described those cell groups in the pancreas which are now called the Islands of Langerhans.

Lepine was the first to suggest that the pancreas furnished an internal secretion necessary for the proper metabolism of sugars and fats. Diamare, Shaffer and others have suggested that the islands are the seat of production of the internal secretion of the pancreas. D'Arnozan and Vaielard, Sscobolew, W. G. MacCallum, and others, have shown that the ligation of the ducts of the pancreas results in the degeneration of the acinous cells which produce pancreatic juice, but that the islet cells remain undisturbed by this procedure.

Since the work of von Mering and Minkowski, hundreds of investigators have attempted to prepare from the pancreas a substance which when administered to diabetic animals would alleviate the symptoms of diabetes. Among these investigators the names of Zuelzer, Scott, Rennie, Murlin and Kramer, Kleiner, Clark, Knowlton and Starling, and Paulesco are prominent. Zuelzer and Scott worked on the hypothesis which was later independently formulated by one of us (F. G. B.). Zuelzer prepared alcoholic extracts of pancreas and administered them to dogs made glucosuric by the injection of epinephrine. He obtained encouraging results for a time but his research was later abandoned. Scott attempted to ligate the pancreatic ducts of dogs but his operations were not successful. He also unsuccessfully attempted to extract the glands with alcohol and we now know that the concentrations he used are unfavorable for the extraction of insulin. Kleiner's experiments with watery extracts of normal dogs' pancreas deserve mention. He obtained some slightly beneficial effects by the administration of these extracts to dia-

betic dogs. His results were not conclusive, however, and his work was not continued.

In 1921 authorities were agreed that all attempts to demonstrate the internal secretion of the pancreas had met with either negative or inconclusive results.

The hypothesis upon which our experiments were founded was that some constituent of the external secretion of the pancreas was antagonistic to the hypothetical internal secretion for which Professor Shaffer of the University of Edinburgh had suggested the name "Insuline". This hypothesis was presented to Professor Macleod of this University and he was able to provide advice and facilities for putting it to the test. Work was commenced in the Department of Physiology on May 16th, 1921. It was originally supposed that only some six or eight weeks would be necessary to test the hypothesis.

In order to eliminate the external secretion of the pancreas it was proposed to take advantage of the above mentioned fact that the acinous cells degenerate after the ligation of the pancreatic ducts. Our first work was therefore to ligate the pancreatic ducts of a number of normal dogs. The animals recovered quickly from the operation and none of them showed any symptoms or signs of diabetes. In the interval required to secure degeneration of the pancreas, we obtained records on totally depancreatized dogs which we contemplated using as test objects. The extreme heat of the summer of 1921 made it very difficult for us to keep the diabetic animals in reasonably good condition and we were not in a position to test any material until late in July.

On July 27th, we decided to make our first test. We anaesthetized a dog whose pancreatic ducts had been ligated some ten weeks previously and removed the degenerated pancreas. The gland was smaller than normal and very firm in consistency. It was immediately sliced into a chilled mortar containing Ringer's solution and the mixture was frozen. After several hours the frozen material was allowed to thaw slowly and the tissue was finely macerated with sand and a pestle. The liquid was then strained off and filtered through paper. This filtrate was the original pancreatic extract used in our experiments. This material was administered by intravenous injection to a diabetic dog. The material exerted a slightly favorable effect upon the blood sugar and sugar excretion of the animal. This experiment was not at all conclusive but extremely encouraging to us, and we made haste to repeat it. Subsequent experiments were very successful and we consistently observed that the administration of this extract of degenerated pancreas resulted in the marked lowering of blood sugar, the diminution of sugar excretion, and phenomenal improvement in the general condition of completely diabetic dogs. The administration of a single large dose of this material often changed a listless semi-comatose diabetic dog into a bright, active animal. Visitors to our working quarters during the months of August and September were greatly impressed with the remarkable effects of this extract. Professor C. L. Starr and Dr. George Young were among the first to witness a demonstration of the beneficial effects of the extract containing the long-sought-for internal secretion of the pancreas. The kindly interest and help of Prof. Henderson was of inestimable value at this stage.

We then proceeded to secure more information concerning the pro-

perties of the extract and its effects upon diabetic animals. It was found that sugar given with the extract was retained to a much greater extent than was the case when it was administered in the absence of the extract. Incubation of the extract with pancreatic juice resulted in the complete destruction of the active material.

When Professor Macleod returned from Europe in September he observed the effects of the administration of the extract. In view of the great importance of the fundamental observation that the active principle of the extract exerted a definite influence upon the blood sugar and sugar secretion of diabetic animals, he advised us to secure even more results along this line. We did this, and in addition were able to show, among other things, that very active extracts could be prepared from other more readily available sources. Active extracts were prepared from the pancreas of foetal calves, taken at a stage of development before the pancreatic ferments had appeared. Potent extracts from normal adult ox pancreas were also secured. To obtain this latter material we extracted finely divided ox pancreas with acidulated alcohol. We consider this a very important experiment since all large scale methods for the preparation of insulin to-day have the acid alcohol extraction as the first step in the process. It was shown that a completely diabetic dog could be kept alive and healthy for at least 10 weeks by the daily administration of this whole gland extract.

The practical application of these results was very evident and in view of this it was deemed advisable to secure the co-operation of other investigators. This was about the middle of December, 1921. Professor J. B. Collip was invited to participate in the biochemical side of the investigation, and was provided facilities by Professor Fitzgerald and Professor Defries of the Connaught Laboratory. A little later Mr. E. C. Noble, Drs. J. Hepburn and J. K. Latchford began work on Insulin under the direction of Prof. Macleod in the Department of Physiology. The work of this group in the winter of 1921-22 resulted in the demonstration of a number of very important facts. It was ascertained that the administration of insulin enabled a completely diabetic dog to store large amounts of glycogen in its liver. It will be remembered that diabetic animals are unable to store greater than 2 per cent. of glycogen in the liver in the absence of insulin even when very large quantities of sugar are administered. It was found that the respiratory quotient of diabetic dogs could be definitely raised by the administration of carbohydrate and insulin. This experiment proved conclusively that insulin caused the burning of carbohydrate in the diabetic organism. The extracts used in the first experiments in which glycogen was found in the livers of completely depancreatized dogs and in some of the respiratory quotient experiments, were prepared from adult ox pancreas by our original method. This group also recognized the deleterious effects of overdoses of insulin and discovered that sugar was a very efficient antidote. The effects of insulin upon various forms of experimental hyperglycaemia were studied, particularly by Mr. E. C. Noble. Drs. Hepburn and Latchford showed that the presence of insulin resulted in the increased consumption of sugar by the perfused mammalian heart.

The first insulin administered to diabetic patients in the Toronto General Hospital was prepared from normal ox pancreas by the original

method. This material exerted a definite effect upon the blood sugar and sugar excretion of a diabetic patient. Certain objectionable effects, however, were observed, which were undoubtedly due to the large percentage of protein which this extract contained.

Professor Collip with the knowledge of the properties of the material which we had obtained and with some additional information which he secured by very extensive work, was able in a very short time to purify the original extract so that much of the objectionable inert material was eliminated. The results of the short study of the clinical effects of this material were reported by Drs. Campbell and Fletcher of the Toronto General Hospital, in collaboration with Professor Collip and ourselves.

It will not be possible, in the space at our disposal, to review in detail the various modifications and improvements which have been introduced in the methods of preparation of insulin. A brief summary of some of the more important contributions is submitted. Insulin was originally prepared from the ox pancreas, as stated above, by the extraction of fresh glands with faintly acid alcohol. The concentration of alcohol in our original experiments varied from 40 to 60 per cent. The alcoholic solution of pancreas was filtered and the filtrate concentrated by evaporation of the alcohol and water in a warm air current. Lipoid material was removed by extracting the residue with toluene or ether. The resulting product was the original whole gland extract. We were able to show that the active material contained in this extract was practically insoluble in 95 per cent. alcohol. Professor Collip used acid alcohol as the initial extractive but raised the concentration to about 80 per cent. By this means certain inert objectionable materials were removed. The inert materials were filtered off and the insulin precipitated from the alcoholic solution by raising the concentration of alcohol to approximately 92 per cent. The precipitated material was dissolved in distilled water. Certain difficulties were encountered when it was attempted to apply this method to a larger scale production and various modifications were introduced by the workers in the Connaught Laboratories in the spring of 1922. It was found that the final product obtained by these methods was not sufficiently pure for prolonged clinical use, and efforts were made to secure a better product. The benzoic acid method of Moloney and Findlay which depends upon the fact that insulin is absorbed from watery solution by benzoic acid was successfully used in the Connaught Laboratories for several months. Professor Shaffer of Washington University, St. Louis, and his collaborators, Somogyi and Doisy, introduced a method of purification which is known as the isoelectric process. This method depends upon the fact that if a watery solution of insulin is adjusted to approximately PH 5 a precipitate settles out which contains much of the potent material and relatively few impurities. Dudley has found that insulin is precipitated from watery solutions by picric acid and he has made use of this fact to devise a very ingenious method for the purification of the active material. Mr. D. A. Scott, and one of us (C. H. B.), who are responsible for the preparation of insulin in the Insulin Division of the Connaught Laboratories, have tested all the available methods and have appropriated certain details from many of these. Several new procedures which we believe are advantageous have also been introduced. The method of preparation of insulin which may be seen in operation at any time in the Insulin Division, is as follows:—

The beef or pork pancreas is finely minced in a large grinder and the minced material is then treated with 5 c.c. of concentrated sulphuric acid, appropriately diluted, per pound of glands. The mixture is stirred for a period of three or four hours and 95 per cent. alcohol is added until the concentration of alcohol is 60 to 70 per cent. Two extractions of the glands are made. The solid material is then partially removed by centrifuging the mixture and the solution is further clarified by filtering through paper. The clear filtrate is concentrated in vacuo to about 1/20th of its original volume. Ammonium sulphate (37 gms. per 100 c.c) is then added to the concentrate and a protein material containing all the insulin floats to the top of the liquid. The solid material is skimmed off and dissolved in water. Certain inert materials are eliminated by adding alcohol to this watery solution so that the concentration of alcohol is approximately 80 per cent. An equal volume of ether is then added to the 80 per cent. alcohol and the precipitate which forms contains practically all the potency which was present in the alcoholic solution. The solution of this precipitate in water is adjusted to approximately PH 5 and a white flocculent precipitate settles out. The solution of this latter precipitate in acid water (PH 2.5) is the final product as it is distributed at the present time.

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Daffydil Night

The Daffydil Committee wish to announce that the performance this year will be held in Convocation Hall on the 7th and 8th of February. This annual event had its beginning in the old Medical School on Gerrard Street twenty years ago. The first performance took the form of a Punch and Judy show in which the professors were caricatured. At that time the professors were not invited to attend this reproduction of their characters. It is reported that on this occasion the proceedings broke up in a small riot. Daffydil, however, did not become an annual affair until 1912. The same year "Epistaxis" appeared as a single sheet.

Last year's production was the best ever staged and it is the aim this year to surpass it if possible. All undergraduates are urged to support the committee and the staff editing "Epistaxis".

Radiologic Diagnosis of Bone Pain

Angela Luong (9T6)

CASE 1

A 55 year-old man presented with unexplained generalized fatigue in association with aching pains localized to the lumbosacral spine, the left thigh, and hips. There were symptoms suggestive of arthritis in the left knee joint. The patient also complained of headaches.

Physical examination was unremarkable except for increased warmth over the affected areas on palpation. Blood tests revealed significantly elevated serum alkaline phosphatase. Serum calcium and phosphorus levels were normal. Radiographs of the head, left femur, and pelvis were obtained, followed by a radionucleotide bone scan (Figure 1).

Based on the history and the radiological results, what is the diagnosis?

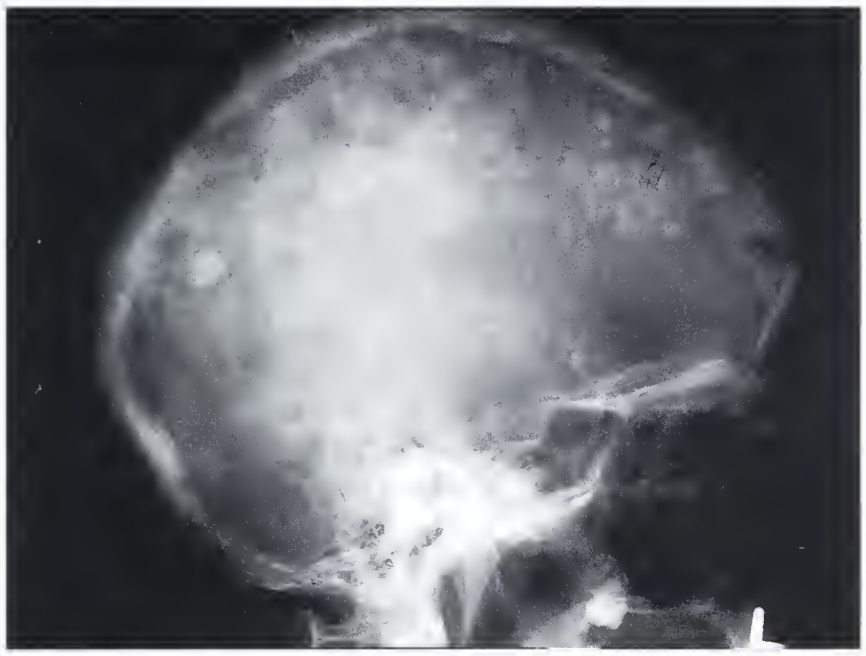

Figure 1a

Figure 1c

Figure 1b

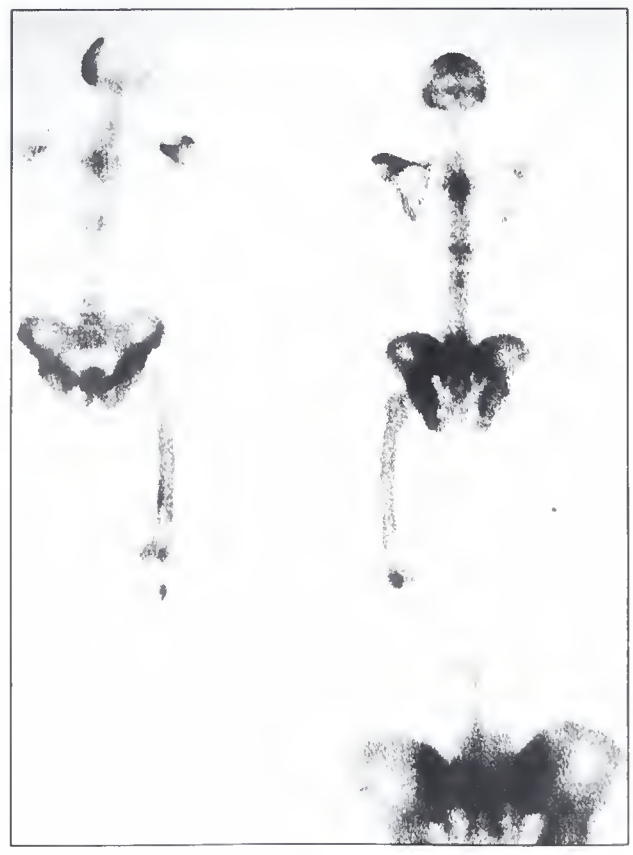

Figure 1d

CASE 2

A 59 year-old man presented 8 weeks post-abdominal surgery with a fever of 39°C and acute onset of back pain. Pain and tenderness were localized in the lumbosacral region, associated with point tenderness and spasm of the paravertebral muscles. Despite the pain, range of motion in the lumbosacral region was preserved. In addition to blood cultures, plain film x-rays and computed tomography (CT) images of the affected regions were obtained (Figure 2).

Based on the radiographic results, what is the diagnosis?

Figure 2a

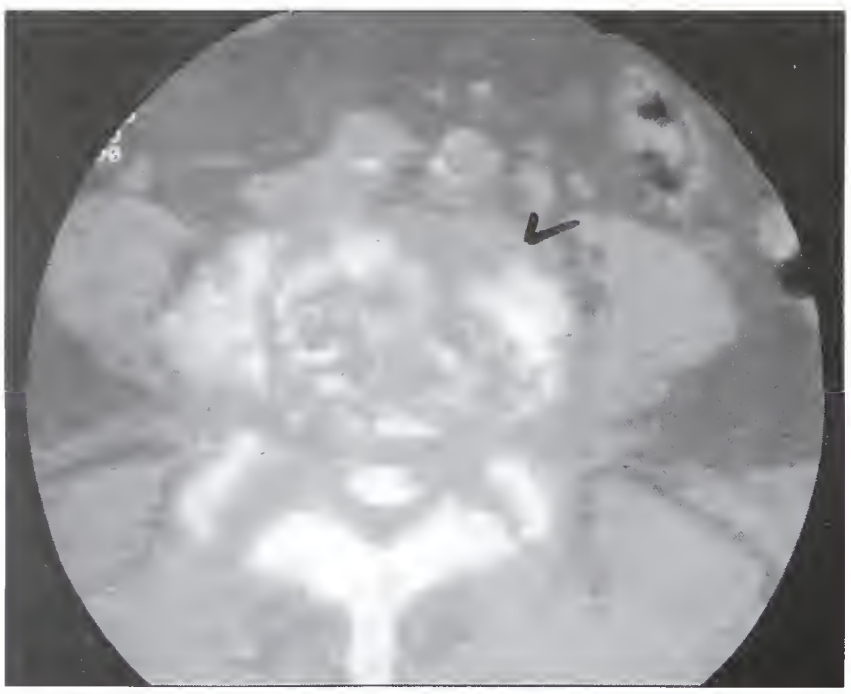

Figure 2b

CASE 3

A 68 year-old previously healthy man presented with back pain localized to the lumbosacral region. He had no history of arthritis or spinal trauma. Physical examination was unremarkable. Plain film radiographs, CT scan, and radionucleotide bone scan of the lumbosacral region were ordered (Figure 3).

Based on history and the images, what is the diagnosis?

Figure 3a

Figure 3b

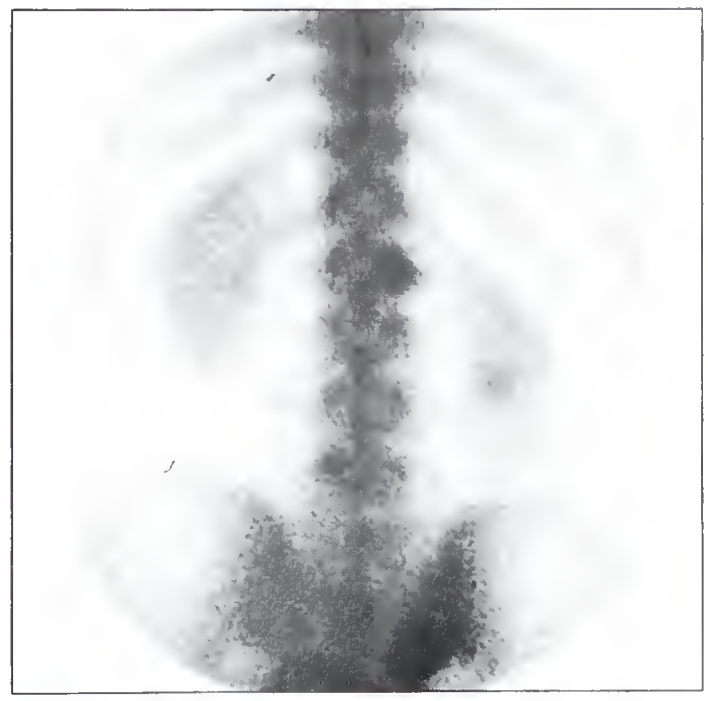

Figure 3c

Answer to Case 1

The clinical signs and symptoms suggest Paget's disease of the bone, also known as osteitis deformans, a chronic disorder of unknown etiology. This diagnosis is reinforced by the imaging studies performed.

Paget's disease is characterized by and believed to be initiated by increased bone resorption associated with proliferation of multinucleated osteoclasts. This is recognized radiographically as the early stage or the destructive phase. In response to the increased bone resorption, osteoblastic activity is also increased, resulting in bone that is haphazard in formation, abnormal in composition, thickened, and structurally weak. The middle stage, also known as the combined stage, displays findings suggestive of combined increases in both resorption and new bone formation. Eventually, some patients progress to the late or sclerotic stage, in which decreased bone turnover produces a picture of burnt-out bone. Although all bones may be affected, the skull, pelvis, femur, and tibia are the most common sites. Rarely, secondary bone malignancy may complicate late-stage Paget's disease.

Radiographically, the skull (Figure 1a) depicts the combined stage of Paget's disease characterized by marked thickening of the entire calvarium with good definition of thickened outer and inner tables. Irregular sclerosis of the thickened bone results in a characteristic "cotton-wool" appearance.

Abnormalities of the long bones such as the femur (Figure 1b) are also commonly observed in the combined phase. There is widening of the bone and thickening of the cortex, along with an accentuated, coarse, lace-like trabecular pattern resulting from abnormally increased bone turnover. Since the resulting bone is weak, fractures are frequent. In this radiograph there is an incomplete fracture (resembling pseudofractures of osteomalacia) seen along the anterior cortex. This most likely represents a stress fracture of the cortex, which tends to heal at the periosteal and endosteal surfaces, leaving a mid-cortical residue. Anterior bowing of the femur can also be seen.

The pelvis (Figure 1c) shows diffuse involvement characterized by cortical thickening and enlargement and a marked coarse trabecular pattern that is visualized on the ischium and ilium. There is also thickening of the pelvic brim.

The radionucleotide bone scan (Figure 1d) is an important imaging modality for the diagnosis of Paget's disease. "Hot spots" resulting from increased uptake of the radionucleotide technetium-99m (^{99m}Tc) are seen in the pelvis and femur and correlate with increased bone turnover activity.

Answer to Case 2

The history should lead one to entertain osteomyelitis of the lumbosacral spine in the differential diagnosis. Although more common in children, in whom the leg bones are usually affected, this infection may also present in adults, often in the vertebral spine. Acute hematogenous osteomyelitis often results from transient bacteremia that seeds microorganisms into the intervertebral space resulting in bone and disc destruction. The most common etiologic agent is *Staphylococcus aureus,* but Gram-negative bacteria such as *Pseudomonas spp.* have also been implicated, especially in the post-abdominal surgery patient. The plain film x-ray of the lumbar spine (Figure 2a) shows narrowing of the L4-5 intervertebral space due to infection at that site. Bony destruction is noted in the L4 and L5 vertebral body end plates.

CT is helpful in evaluating patients suspected of spinal osteomyelitis because of its ability to detect early vertebral bone erosion, disk involvement, adjacent soft tissue swelling, and extension of the process into the spinal canal. CT examination (Figure 2b) of this patient shows bone erosion and paravertebral soft tissue swelling. A percutaneous needle biopsy of the disc space under CT guidance would also be indicated in the event that blood cultures were negative.

Answer to Case 3

This case is a classical presentation of osteoblastic metastasis from carcinoma of the prostate, which is the most frequently encountered cause of osteoblastic metastases in men. Radiologically, poorly defined areas of increased density are observed initially which may progress to complete loss of architectural landmarks. Lesions may present as discrete foci of various sizes with ill-defined borders or as a diffuse area of sclerosis.

On the plain film (Figure 3a), there is a sclerotic lesion of the right pedicle of the L1 vertebral body. This is also observed on CT (Figure 3b) where the pedicle involved is associated with an abnormal increase in density. This is again confirmed by the ^{99m}Tc radionucleotide bone scan (Figure 3c) where the posterior view indicates a "hot spot" at the right L1 pedicle. Furthermore, increased radionucleotide uptake is also noted in the sacrum to suggest areas of osteoblastic metastasis.

Acknowledgements

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